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PANEL DISCUSSION ON THE CLINICAL MANAGEMENT OF MYOCARDIAL INFARCTION*

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MODERATOR WRIGHT: The members of the panel will try to make this discussion of the clinical management of myocardial infarction as practical as possible, and to evaluate evidence that has been presented for some new ideas regarding this disorder and its treatment.

The panelists represent a wide variety of disciplines in this general field. Their views will vary on certain subjects.

In order to cover our subject systematically, I shall ask for opinions on a number of key questions and try to obtain the opinion of more than one person on most of these issues.

If you have questions that you would like to submit from the floor, and if time permits, we shall be glad to answer them. I shall assign them to members of the panel.

My first question has to do with rest. I start with rest because every report on the care of a patient with myocardial infarction recommends rest. Accepted practice has been to put the patient to bed for as long as three months, and later for one month. In recent times, however, questions have been raised by Dr. Levine of Boston and others as to how long the patient should remain at rest. I shall ask Dr. Howard Sprague, who also comes from Boston, for his views as to the present status of rest as a form of therapy for myocardial infarction.

DR. SPRAGUE: You mean, then, what are my views, not what are the views of Boston?

MODERATOR WRIGHT: I should like to have your own views, and then you may enter into a general discussion, if you wish.

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DR. SPRAGUE: Whatever I say will imply that I individualize the management of each patient. We cannot write a formula to cover every patient with myocardial infarction. I agree that the pendulum has swung to the point where myocardial infarction is treated more casually than previously with regard to early ambulation.

The duration of bed rest should depend upon the degree of reaction of the individual patient. As Dr. Levine has pointed out, we should not place every patient in a chair the day after an acute myocardial infarction. In general, I recommend three weeks at rest, but I often allow the use of a commode chair by the bed after the first week. Ambulation can be accomplished in easy stages, with dangling the legs over the bedside, sitting in a chair, and staying up by the end of the third week. The degree of pressure under which the patient labors determines the rate at which he may be allowed to resume activity.

I think in terms of a total of three months away from the job, if it can be accomplished.

MODERATOR WRIGHT: You imply a possible difference between your views and those of physicians in Boston in general.

DR. SPRAGUE: No. I said that I cannot speak for Boston.

MODERATOR WRIGHT: Dr. Ernstene, what are your views with reference to rest for the patient with a myocardial infarction?

DR. ERNSTENE: I, too, would like to emphasize the fact that the treatment of each patient represents an individual problem. One of the most significant recent advances in the treatment of myocardial infarction has resulted from redefinition of the term "rest," and what it implies. We usually plan to have the average patient up in a chair at the bedside by the third or fourth day after the onset of the attack. However, it should be pointed out that chair treatment is *not* early ambulation. The patient is helped in and out of bed and is allowed no other privileges except the use of the bedside commode. By the end of three weeks, the average patient can safely be allowed to take a few steps to the bathroom. At the end of six weeks, a further gradual increase in activities is permitted, the rate of increase being determined by the presence or absence of symptoms referable to the heart. We hope to have the average patient back at work at the end of three months.

MODERATOR WRIGHT: Dr. Friedberg, have you any additional comments?

DR. FRIEDBERG: First, we ought to have a rationale for resting the patient before we determine how to rest him and for what length of time. Obviously, when a person has a damaged heart, we think that the less the heart is subjected to strain, the less risk there will be. To be more specific, a certain percentage of the mortality results from rupture of the heart. The thought has been that activity might increase the risk of rupture.

I should say, without going into detail, that a great deal of evidence indicates that unless activity is violent or gross in nature, it is not an important factor in the occurrence of ventricular or septal rupture. Of importance, among other factors, are the nature of the infarct, the distribution of the blood supply, and the presence or absence of hypertension. The fear of myocardial rupture due to activity is greatly exaggerated.

The rationale for bed rest, or for rest in myocardial infarction involves the assumption that a certain period of time is required for the formation of a good scar. Unfortunately, only scanty evidence for this exists. The few studies that have been made seem to indicate that the development of scar tissue requires between three and six weeks. The latter date appears to be the more reliable for formation of a good scar. This has been the basis of the six-week rest program so commonly used.

Moreover, experimental evidence indicates that when coronary thrombosis with myocardial infarction is produced in a dog, the scar will be stronger and there will be less tendency for formation of an aneurysm, if the dog is rested rather than subjected to exercise.

The complications that occur in human coronary thrombosis and the associated morbidity and mortality seem less related to inadequate rest than to many other factors—notably thromboembolic phenomena, which are more likely to be favored by bed rest than the reverse. The swing toward liberalizing activity has been based on this factor more than on any other.

I am leading up to the question of chair rest and bed rest from this point of view. A patient with an acute myocardial infarction, who has heart failure and is therefore orthopneic, obviously will feel better in a sitting or standing position than if recumbent. Such a patient is placed in a chair because that is the best way to treat his heart failure, but no special merit has been demonstrated for chair rest for a patient who has an acute myocardial infarction without orthopnea.

Dr. Ernstene indicated, as Dr. Levine has often stressed, that placing a patient in a chair does not imply early ambulation; it is merely putting him in the upright position, with assistance. That implies danger from ambulation.

I hold the reverse opinion. I object to chair rest because it seems an unfortunate way to avoid the very ambulation that is the objective sought in trying to avoid the risks of bed rest. I prefer to let the patient with an acute myocardial infarction, perhaps once a day, take a few steps to the commode or even to a lavatory (if it is close by and he is not too ill) in an effort to obtain some degree of early ambulation. Chair rest is not early ambulation and I do not worry about the activity involved in placing the patient in a chair, but I *am* eager that he should have some degree of ambulation.

With this as a background, I would recommend the following general routine. Unless the patient is ill or has complications, there should be a period of about six weeks during which the patient is markedly restricted from going out of his room, indulging in activities, and talking to business associates. Frequently, the family asks that no visitors be allowed, except from the family. However, from the point of view of mental stress, the risk is from the family and not from other visitors. Therefore, I tend to keep the family out as much as possible. Otherwise, I let the patient proceed according to how he tolerates visitors and enjoys them.

Many patients who are placed in a chair, with the idea that they could sit all day, have looked longingly at the bed. As a matter of fact, that is as likely to happen as for a patient who is in bed to look longingly at a chair.

MODERATOR WRIGHT: Various views have been expressed. I am more conservative than Dr. Ernstene about letting patients out of bed. We do allow many out

of bed slowly and carefully after ten days or two weeks, whereas formerly it was three or four weeks.

DR. SPRAGUE: The patient can exercise in bed. I like to have him do that as soon as possible. I disagree with the practice of feeding the patient and not letting him lift his arms over his head.

MODERATOR WRIGHT: That is right. I intended to raise that question with reference to Dr. Friedberg's remarks. Instead of getting patients up and making them walk around, I have adopted the practice of having them exercise their feet and calves and move their legs under direction. I tell them to move their legs, if they are able, from 100 to 500 times a day—at any rate to move them often, so that they do not lie for hours with their legs still.

If they are under too much sedation, they will not move their legs and not want to sit up. Excessive sedation should be avoided. Only enough should be used to keep the patient at relative rest and to relieve him of pain which produces anxiety. Is this the consensus? Does anyone want to comment further on sedation?

DR. SPRAGUE: I should, to the extent that I think the physician should realize the amount of sedation he can give the patient by taking a little more time at his morning visit, and reassuring the patient that everything is going all right. Similarly, I think a good nurse is much more useful than a lot of sedatives.

MODERATOR WRIGHT: Yes, we need many more good nurses. This is a critical need today.

DR. ERNSTENE: One of the most important advantages of the chair treatment lies in the emotional or psychologic sphere. The former treatment of acute myocardial infarction by strict immobilization in bed was ideally contrived to generate insecurity in a patient's mind. It often took a great deal of reassuring by the physician and the patient's family to relieve it, and it unquestionably had a retarding influence upon the patient's recovery.

MODERATOR WRIGHT: Practically every statement made thus far has been like a two-headed coin. For instance, some patients who do not happen to have pain and can sit up in a chair, simply cannot understand why they cannot get up and start walking around. I have found it more difficult to discipline patients in a chair than when they were kept in bed. The physician must use his best judgment. The views of the panel, in general, seem toward liberalization of activity as compared with ten years ago.

DR. FRIEDBERG: We should emphasize that orders for opiates written the day that a patient comes into the hospital should not be left as standing orders. I often find patients who are virtually comatose by morning. They had pain in the late afternoon. There was an order for ¼ grain, or 15 mg. of morphine every four hours, for pain and therefore they received that dosage more or less routinely. Neither do I like to leave orders for precautions for every patient, because that very thing negates the advantage of a patient moving around in bed. The nurses begin to think that the patient should not budge, turn, reach for the phone, and so forth.

MODERATOR WRIGHT: Our next subject is the use of oxygen. Dr. Friedberg,

how often do you use oxygen? In what percentage of your patients? How do you decide which patients require it? Are you liberal in your use of oxygen, or do you use it infrequently?

DR. FRIEDBERG: This, too, will be a double-faced coin. In the first place, I am not an enthusiast about oxygen. In patients with pulmonary complications, or shock with obvious cyanosis, there is no question as to its value. Aside from use in patients with these complications, I doubt that oxygen therapy has much value. Nevertheless, I do use oxygen—much more often than necessary from a therapeutic point of view. It should not be given to a patient who has had pain but who feels well and comfortable, because it has certain frightening psychologic aspects. If, however, the patient still has persistent severe pain, administration of oxygen is advisable. There is terrific pressure to use oxygen. It is hard for me to disprove that it has merit, and so I shall merely say that I use it more often than I think it helps. I have often had the impression that the oxygen tent has greater merit than the other methods of administration, even though higher concentrations of oxygen can be obtained with the use of a mask. Perhaps because of the air-conditioning effect and the temperature control, patients are afforded more comfort.

MODERATOR WRIGHT: We use oxygen more often in the summer than in the winter months for that reason. If the humidity and the temperature are high, this type of patient is more apt to become breathless.

Dr. Ernstene, have you any comments on the use of oxygen?

DR. ERNSTENE: We use it only when certain indications are present—severe dyspnea, cyanosis, or intense and prolonged pain.

One often encounters considerable difficulty in convincing the house staff that oxygen should not be used routinely. I agree with Dr. Friedberg as far as indications are concerned, but we apparently use it much less frequently than he does.

DR. SPRAGUE: I agree on one point—it is extremely important that the oxygen tent be kept cool. That the cardiac output under conditions of heat is much greater than if the patient were walking around is sometimes forgotten. Perhaps, as yet, we have not used enough hypothermia in the treatment of this disease.

DR. FRIEDBERG: May I ask a question? You use oxygen if the patient is dyspneic. In most forms of dyspnea, there is no significant reduction in the oxygen saturation of the arterial blood. May I ask the rationale for this?

DR. ERNSTENE: Persistent dyspnea usually results from left ventricular failure and pulmonary congestion. Oxygen frequently provides great relief from the shortness of breath.

MODERATOR WRIGHT: We shall now discuss various forms of medication. Aminophylline has been recommended for prompt administration. Dr. Sprague. do you use aminophylline? I shall not use the word "routinely" and nobody in this panel hereafter need say "we individualize for each patient." Let that be understood and we shall save verbiage. Do you use it in the treatment of acute myocardial infarction?

DR. SPRAGUE: Rarely.

MODERATOR WRIGHT: How do you know when to use it?

DR. SPRAGUE: I shall tell how it has been used in my experience. A resident usually has given it before I arrive!

MODERATOR WRIGHT: Dr. Ernstene, do you use aminophylline?

DR. ERNSTENE: We use it only in patients who present evidence of acute left ventricular failure with severe dyspnea.

MODERATOR WRIGHT: Dr. Friedberg?

DR. FRIEDBERG: I do not use it frequently, despite the work of Gilbert and his co-workers, who tried to show that the blood flow is increased. I use it occasionally in two situations. I administer it to patients in whom a large bronchospastic element accounts for the dyspnea. For example, in many early cases of acute left ventricular failure, rhonchi and wheezes can be heard; this means that, whatever the initial mechanism, bronchospasm is present. It would not be advisable to use epinephrine, but I do use aminophylline intravenously. I also use it in patients with coronary occlusion who have Cheyne-Stokes respiration.

MODERATOR WRIGHT: Dr. Stamler?

DR. STAMLER: Permit me—relatively early in the discussion—to clarify my situation. Unlike my colleagues here, I am not a practicing cardiologist. Hence, I cannot bring to bear, on these clinical problems of management of acute infarction, judgment seasoned by experience. Under the circumstances, I should like merely to pose one question. Does not a certain risk attend the intravenous administration of aminophylline in persons with increased myocardial irritability under these circumstances?

DR. FRIEDBERG: That brings up the question as to whether to use it intravenously or rectally by suppository. I occasionally use aminophylline suppositories in patients having *acute* attacks of nocturnal dyspnea, for example. I use it intravenously in patients with acute left ventricular failure who have not responded satisfactorily to, let us say, morphine and oxygen.

MODERATOR WRIGHT: Accidents have been reported. Have you observed any on your extensive service?

DR. FRIEDBERG: I have encountered none. I think accidents are caused by too-rapid intravenous injection.

MODERATOR WRIGHT: Has anyone here encountered accidents from the injection of aminophylline?

DR. SPRAGUE: No fatal accidents. I agree that it is a question of rapid injection. Dr. Weiss used to say that you could put anything into a vein, if you took your time about it.

MODERATOR WRIGHT: Let us now consider the use of nitrites. There are long-acting nitrites, so-called because of their relatively slow rate of absorption and apparently prolonged action. In contrast, we have nitroglycerin, which acts promptly. We are talking, not about the symptom of angina pectoris, but about the treatment of myocardial infarction. In the treatment of myocardial infarction, do you think that there is a place for nitroglycerin, and do you use it? Dr. Ernstene?

DR. ERNSTENE: Has the diagnosis of myocardial infarction been made?

MODERATOR WRIGHT: Yes.

DR. ERNSTENE: Then, I think it has no place in treatment except in the rare

patient who experiences angina pectoris while at rest during his convalescence from acute infarction.

MODERATOR WRIGHT: Assuming that one branch of a coronary artery is blocked and early myocardial infarction ensues, will nitroglycerin relax other collateral vessels so that more blood will enter the primary infarcted area?

DR. ERNSTENE: Because the effect of nitroglycerin is so short lived, I doubt that it would be of benefit. On the other hand, it has been suggested that any retarding influence on coronary blood might favor propagation of the original occluding thrombus.

MODERATOR WRIGHT: You mean that, by dilating the vascular tree generally, you may actually decrease the coronary flow rather than improve it?

What about this, Dr. Sprague? How do you use nitroglycerin in this situation?

DR. SPRAGUE: A certain degree of apprehension is justified. Last week, when I was away, one of my patients who had never taken nitroglycerin, received it for angina. He had a prolonged attack and went to a local physician, a young man just starting his practice in the town. He gave the patient nitroglycerin tablets in his office. The man promptly collapsed and had a fine myocardial infarct.

My experience with nitroglycerin is this: It may be prescribed for pain without hesitation when a myocardial infarct develops in a patient accustomed to taking nitroglycerin for angina, or during the convalescent stages of infarction, but not in the state of extreme collapse. We had an experience in which nitroglycerin was given on an hourly basis to a medical colleague, who had a myocardial infarct apparently involving the septum, with heart block. Nitroglycerin therapy obliterated the attacks of syncope during the course of the myocardial infarct.

MODERATOR WRIGHT: The point illustrated by the case you mentioned—the giving of nitroglycerin when a person has had an infarction, particularly if the blood pressure is dropping—is well taken. A sudden additional drop in pressure may produce a catastrophic effect. Therefore, we are reluctant to give nitroglycerin, when real evidence of infarction exists.

Have you any comments, Dr. Stamler?

DR. STAMLER: I think that the reluctance mentioned is general.

DR. FRIEDBERG: Although the risk in administering nitroglycerin to a patient with a myocardial infarction has been stated several times, most patients who have had angina pectoris and then acute myocardial infarction *do* take nitroglycerin, and may take many tablets. In fact, this is often the reason that the patient knows that the cardiac condition is not angina pectoris but acute myocardial infarction. Considering the frequency with which patients take nitroglycerin at the onset of acute myocardial infarction, it is probable that this drug rarely produces shock. However, if the presence of an infarct is certain it is better to avoid nitroglycerin.

MODERATOR WRIGHT: Your position is well taken. In actual practice, most patients receive at least 1 nitroglycerin tablet before they see the physician who makes the diagnosis of myocardial infarction. However, once the diagnosis is made, there should be reluctance and caution in the use of nitroglycerin. This panel appears to agree that it should rarely, if ever, be used for acute infarction.

What about longer-acting vasodilators, such as Nitroglyn or Peritrate? Would anyone like to take a position with reference to them? Dr. Sprague?

DR. SPRAGUE: I do not use them during the course of an acute myocardial infarct.

MODERATOR WRIGHT: Do you use them for angina?

DR. SPRAGUE: Yes.

MODERATOR WRIGHT: Do you think the evidence as to their value is sound?

DR. SPRAGUE: I don't know what sound really means. It seems to depend upon the patient. Some patients appear to improve. Dr. Friedberg will remember the exhibit in Havana last week wherein it was pointed out that Peritrate should be taken before and not after meals.

MODERATOR WRIGHT: Dr. Ernstene?

DR. ERNSTENE: I think that the long-acting so-called coronary dilators have no part in the treatment of acute myocardial infarction.

MODERATOR WRIGHT: Does anyone here think they do?

If not, we shall consider digitalis. The question of its use constantly confronts the physician. What are the indications and contraindications for digitalis in the treatment of acute myocardial infarction? Dr. Friedberg?

DR. FRIEDBERG: In general, the indications for digitalis are congestive heart failure and certain arrhythmias, considered in the special setting of acute myocardial infarction. Heart failure denotes more than is implied by the term acute myocardial infarction. The indication for digitalis is clear when frank left and right-sided heart failure develops in a patient who has had a previous infarct, has a large heart, and perhaps had heart failure previously.

On the other hand, there is the patient who has acute myocardial infarction. The heart is of normal size. Failure is confined to the left ventricle, and is of the acute type associated with cardiogenic shock or cardiac injury, which really consists of redistribution of blood when there is congestion behind the acutely failing left ventricle. In such patients, there is no indication for the use of digitalis because of the acute left heart failure, if it is mild or if associated with shock without pulmonary edema.

If, during the first week after infarction, there is water retention or nocturnal dyspnea, the heart-failure rule for therapy should be applied. Some of these patients have arrhythmias—frequently, paroxysmal atrial fibrillation. As a rule, nothing need be done for this condition, because it usually subsides in a few hours. If the rate is alarming, and if this in itself seems to be causing heart failure, the patient should be rapidly digitalized.

These are the essential indications. Everything else is virtually a nonindication or a contraindication.

MODERATOR WRIGHT: Dr. Ernstene, what have you to say about digitalis?

DR. ERNSTENE: I think a bit differently about the treatment of acute left ventricular failure. In my opinion, left ventricular failure after acute myocardial infarction is an indication for administering digitalis.

As to the other indications for using the drug, I agree with Dr. Friedberg.

MODERATOR WRIGHT: Dr. Sprague?

DR. SPRAGUE: I hold an intermediate opinion. I hesitate to give digitalis during

the most acute stage. I rely more on mercurial diuretics and manage without the use of a potentially toxic drug during the time of great ventricular irritability. In other words, if I were forced to use digitalis, I would perhaps use it on the second rather than on the first day.

DR. FRIEDBERG: May I make a slight revision in what I said? In the early acute stage of infarction, in the patient with acute left ventricular failure and pulmonary edema who has not responded to morphine and oxygen and sometimes aminophylline, I do use a rapidly-acting digitalis preparation virtually as an emergency measure. Every once in a while, whether due to the digitalis or coincidentally, there is a dramatic effect. In acute left ventricular failure at the very onset, I have misgivings about introducing digitalis, but I give it if I find that I am losing out and the patient is not making headway.

MODERATOR WRIGHT: Dr. Friedberg, we want to make this discussion as useful as possible to our audience. When you say you use rapidly-acting digitalis, what are you talking about?

DR. FRIEDBERG: The drug and dosage in acute left ventricular failure will depend upon the degree of emergency. In an extreme emergency, I may use 0.25 mg. of ouabain (a strophantus preparation) and perhaps repeat this dose in an hour; or repeat 0.1 mg every half to three-quarters of an hour after that until I have given between 0.5 and 1.0 mg.

MODERATOR WRIGHT: Is this intravenous medication?

DR. FRIEDBERG: It is all intravenous in the emergency treatment of acute left ventricular failure that has not responded, usually at the onset of the condition. If I think that the patient is not responding but believe that a matter of an hour or so will not decide his fate, I use Cedilanid in doses of 2 or 4 cc., wait an hour, and then give another injection of the same drug.

MODERATOR WRIGHT: Why don't you use ouabain for those cases too? Do you think ouabain is more dangerous than Cedilanid?

DR. FRIEDBERG: Of course this is all traditional, but I have the impression that it is more dangerous. Every once in a while I hear of, or see a patient in whom a complication, an accident or even a fatality has been attributed to ouabain. I do not recall such an occurrence in connection with Cedilanid.

MODERATOR WRIGHT: Do you, Dr. Ernstene or Dr. Sprague, have any comments to make about the use of different types of digitalis preparations or digitalis-like preparations? What do you use?

DR. ERNSTENE: Are you talking about intravenous preparations?

MODERATOR WRIGHT: Either intravenous or oral.

DR. ERNSTENE: With reference to intravenous preparations, I think that a great deal of the apprehension about ouabain has been due to lack of acquaintance with the proper dosage. When ouabain is given in the manner outlined by Dr. Friedberg, it is perfectly safe. Lanatoside-C, however, is a safe and preferable preparation because it can be given in larger amounts; this lessens the possibility of error in dosage.

As for oral preparations, I still believe that tablets composed of whole leaf are just as effective as any of the purified preparations and often have the advantage of being much less expensive.

MODERATOR WRIGHT: Are they equally free from causing digestive disturbances?

DR. ERNSTENE: When given in proper dosage, I think they are.

MODERATOR WRIGHT: Dr. Sprague?

DR. SPRAGUE: We use Cedilanid almost exclusively for intravenous administration. About thirty-five years ago, the death of a patient at the Massachusetts General Hospital was attributed to strophanthin; being traditional, we have not used it since.

MODERATOR WRIGHT: Conceivably, the patient did not die because of the strophanthin.

DR. SPRAGUE: This is quite true.

MODERATOR WRIGHT: Dr. Stamler, have you any comments on these drugs?

If not, I am sure that the audience will be interested in other drugs, and I hope will write questions regarding them.

We shall proceed to tobacco. What do you do about the patient who is a heavy smoker, has myocardial infarction, and is brought into the hospital but receives no oxygen. Obviously, if he receives oxygen he cannot smoke, but what about this situation, Dr. Sprague?

DR. SPRAGUE: He may not smoke, as far as I am concerned.

MODERATOR WRIGHT: You make them all stop?

DR. SPRAGUE: Yes.

MODERATOR WRIGHT: Dr. Ernstene?

DR. ERNSTENE: I do the same.

MODERATOR WRIGHT: Dr. Friedberg?

DR. FRIEDBERG: I make them stop if I can, but don't ask me to give all the evidence.

MODERATOR WRIGHT: We are not asking for evidence, because that would require volumes. You are among the most experienced of cardiologists, and I am sure that you have made a decision based upon what you consider to be the best evidence. We do not take pleasures away from patients for the fun of it. We only take away something that a man cherishes as much as his cigarettes, if we are convinced it is for his good and may influence the outcome of a serious condition. Dr. Stamler?

DR. STAMLER: Let me reiterate that, unlike the other panelists, I view many of the problems of the treatment of acute myocardial infarction from a distance, as I am not active on a clinical service. From my limited direct experience and from my knowledge of the literature, I am convinced that—with few exceptions—the sound procedure is to stop smoking.

MODERATOR WRIGHT: Yes.

DR. SPRAGUE: I shall tell why I do it. If a man can stop smoking, recover from a myocardial infarct, stay away from tobacco, and reduce his weight or not gain weight, this furnishes important evidence of his motivation to play the "game" therapeutically as I know it in 1956. The man who says, "I cannot stop smoking," "Don't do this to me," and so on, does not have the backbone to play the "coronary game" well.

MODERATOR WRIGHT: You are right. We stop them. We do so promptly, because this may represent the golden opportunity if we are planning to have a patient stop smoking. He is in the hospital. We can keep cigarettes out of his room. We not only prevent the patient from smoking, but we put a sign on the door prohibiting smoking in the room. The patient is handicapped if his wife and others are permitted to smoke in his room while he is trying to stop. This can be enforced, and it also impresses the family with the importance of eliminating smoking. If the patient is in an oxygen tent, it is easy.

Immediate discontinuation of smoking gives the patient the advantage of three weeks to a month of hospital discipline. If he smokes again after that regimen, you probably can't stop him at home. Frequently the opposite proves true. The person whom you have been unable to persuade to stop smoking at home, probably will stop at the time he has a myocardial infarct, if you insist. Frequently, he will not smoke again; for most patients, this is probably beneficial, as far as we can tell from the evidence today. It cannot result in harm.

We come now to the subject of anticoagulants. As you know, it has many facets. We have allowed time to discuss anticoagulants and the problems of diet and cholesterol, since they appear to be an advance over and above what might be called fairly routine therapy.

The facets are reflected by the following questions: Do you use anticoagulants in any patients? Do you use them in all patients on your hospital service unless there are contraindications? If so, what anticoagulants do you use? Do you use them in prophylaxis, or only for acute myocardial infarction? Do you use them later on a long-term basis for the prevention of future infarctions?

Let us first discuss the question of whether or not to use them in the treatment of myocardial infarction and, if so, how to select cases. During the last year, in what percentage of patients with a definite diagnosis of myocardial infarction did you use anticoagulants? Dr. Sprague?

DR. SPRAGUE: We shall become involved in difficulties here. In the first place, what is a myocardial infarct, and how do you know that one is, or is not, present? It would appear from pathologic studies and correlation with clinical syndromes that, as the British have recently said, "Any pain of cardiac or coronary origin that lasts longer than half an hour represents a myocardial infarct." In many such instances the condition may turn out to be what I call a T-wave myocardial infarct, but I think it is still a myocardial infarct.

If this be true, such a patient should be treated in a hospital. However, when this is the whole pattern, with perhaps some minor necrosis indicated by the results of such determinations as transaminase and sedimentation rate, or if the fever is only slight, the patient should not receive an anticoagulant. I am not a thorough-going antagonist of the use of anticoagulants, but I do not use them routinely. I try to exercise judgment, although some of my friends say that this is impossible and that you cannot tell when a mild myocardial infarct may become a severe one. I am still clinically-minded enough to think that, by and large, I can. When there is such a large area of disagreement, I allow young men on my service to make the decision. When I am on the service, few of my patients

receive anticoagulants unless the resident is eager to decide whether or not it is advisable. Dr. Bland, who is on a ward across the corridor, administers anticoagulants to most, if not all, of his patients.

The mortality rates do not seem to differ much. I have not analyzed them, so I cannot tell you the percentages. I mistrust statistics in this particular problem, but shall not relate my reasons. Anticoagulant therapy is indicated in the patient who has had a previous myocardial infarct, is admitted in a state of shock, has to lie inertly by virtue of the severity of the disease, and has congestive failure, an elevated temperature and persistent pain. Neither anticoagulants nor any other medicine should be given merely because of social pressures or, let us say, feelings that make the physician try to protect himself against his own clinical judgment that there should not be routine use of any medication.

MODERATOR WRIGHT: Dr. Ernstene?

DR. ERNSTENE: When one does not use anticoagulants in the so-called good-risk patient, and the patient dies suddenly, one cannot help but wish that such therapy had been employed. Because of an experience or two of that kind, I now use anticoagulants in all patients who do not present a specific contraindication to their employment.

MODERATOR WRIGHT: Dr. Friedberg?

DR. FRIEDBERG: Rest is one of the few measures in the treatment of myocardial infarction about which I have no misgivings as to its indication and value. I am not certain that bed rest will change the mortality rate. Only a comparison with the results in institutions where patients are allowed to thrash around would indicate whether there is any greater risk of cardiac rupture if patients are not put to bed. I put them to bed because it seems reasonable and traditional.

As for the treatment of patients with anticoagulants, it is about the only measure for which we have really good evidence of usefulness. I certainly sympathize with misgivings about statistics, but these statistics are really of a very special and impressive type. They are impressive, first of all, by their very consistency. It is not as though one could marshall a large group of data indicating that anticoagulants reduce mortality or thromboembolic complications, and then could marshall an equal amount of data to the contrary. The reverse is true. When anyone has doubted it and proceeded to make the control studies with and without anticoagulants (to the extent that it is possible), the results always have been the same. For example, among the 21 series that Dr. Wright and his associates surveyed—I am not referring to their own report of 1,000 odd cases—there were 19 series in which mortality was reduced between 50 and 200 per cent. The statistics become even more impressive, if the figures are revised to include only the period in the disease during which anticoagulants would be effective. There was a certain mortality during the first two days before anticoagulants could exert their action. If these data be omitted, the figures are even more uniformly in favor of the effectiveness of anticoagulants.

I have not reviewed the other 2 of the 21 series for some time. If I recall correctly, 1 series without controls was reported from Texas. A pathologic index was devised to suggest what the mortality should be. Then, it was shown that the

actual mortality was about what it should have been on the basis of the calculated index. The other study was made in Boston, Dr. Sprague. The difficulty with this study was that, whenever a patient was very sick, controls were abandoned and anticoagulants were administered.

In our own hospital, some years ago, the chief of one service was unwilling to accept the statistical evidence favoring the use of anticoagulants. It was agreed that only patients admitted on alternate days would receive anticoagulants. Patients referred to the service of the man opposed to anticoagulants were not to receive these drugs, whereas those assigned to other services would receive them. Thus on Monday, Wednesday and Friday, patients with myocardial infarction received anticoagulants. On Tuesday, Thursday, Saturday, and alternate Sundays, they did not. After a period of two or three years, data were accumulated. It is true that the control was not good, for the simple reason that physicians in the community, including many who in public objected to anticoagulants, were careful not to send in their patients—their sick patients at least—on the days when they were not to receive anticoagulants. Despite this weighting, the mortality was twice as high in the group that did not receive anticoagulants.

I may have clinical misgivings about statistics, and I certainly am not one to believe all statistics. However, we have so much more basis for a decision as to whether or not to use anticoagulants than we have for almost any other measure, be it morphine, oxygen, rest or nitrites, that I do not see why there is any real resistance other than that caused by certain inconveniences, expense, and having to worry about determining the prothrombin time. These disadvantages are real, but we ought to make some effort to eliminate them rather than abandon the use of anticoagulants.

MODERATOR WRIGHT: Dr. Stamler, would you like to comment on this?

DR. STAMLER: I should like to speak for myself, on the basis of having been at Michael Reese Hospital, Chicago, in the last year of participation in the cooperative study. I came to Michael Reese in 1948. At that time, the conjoint study was still in progress. Under Dr. Katz's direction physicians at Michael Reese studied what was probably the largest number of patients observed in a single hospital. Although I did not participate in that investigation, I was close enough to it to be impressed by the trend of the results. Since then, I have keenly followed the continuing debate, which by now—I think you will agree—is not always as objective and scientific as it might be. This situation is like many others in medical research. What is viewed at first as a definitive answer ultimately may not turn out to be that. The fact is that some responsible workers are posing serious questions about anticoagulants that cannot be lightly dismissed. I hasten to stress that, nevertheless, the accumulated data in support of the value of anticoagulants are such that at present the burden of proof would seem to rest with those who question their demonstrated utility in the treatment of *acute* myocardial infarction. It is a fairly impressive story.

In view of present trends, it is worth adding that *long-term* therapy of coronary disease with anticoagulants is still at the stage of clinical investigation, although several papers reporting positive results have appeared recently.

MODERATOR WRIGHT: Perhaps I should say a few words, although the mention made regarding my part in the development and evaluation of this form of treatment may make this seem unnecessary. However, it is of some interest that as time has passed confirmatory results have been reported in more than 50 series of patients, not only from centers in the United States, but also from other parts of the world. A large group was reported in Basle at the Conference on Thrombosis and Embolism in 1954.

I have just returned from Moscow where I attended the Fourteenth Congress of Internal Medicine of the Soviet Union. I did not know why I was invited, but after I arrived, I found out. One of the reasons was that they planned to present their first comprehensive surveys on the use of anticoagulants. Unknown to us (although we had heard rumors that occasionally Dicumarol was given to patients), a series of studies had been set up in the U.S.S.R. The results were reported in nine papers at this congress. These papers were presented from centers in the Ural Mountains, Moscow, Leningrad, Stalingrad, Peking, and several other cities. They had tried to follow our procedures. They were thoroughly familiar with our studies. The results were almost the same as ours. This makes a total of approximately 60 confirmatory reports, based on studies in different parts of the world. Against this, are 4 or 5 borderline reports, but in some of these the statement is made that the study was not set up satisfactorily for what the authors were trying to accomplish. Unless the proper methods are developed for conducting such a study with suitable controls, one cannot expect to obtain valid data. Unfortunately, this principle is too often neglected in our literature.

A point that we must consider is the fact that different, and in some instances questionable and vague, criteria for myocardial infarction are being utilized in some studies. When the Committee of the American Heart Association established criteria, they made certain that the cases accepted for study had definite myocardial infarction, as far as could be determined and beyond reasonable doubt. It was recognized that if borderline or questionable cases were included it would later be pointed out that many of the cases were not true myocardial infarction, and that, therefore, the data would be invalid.

However, it is true that there are all degrees of infarction, many of them microscopic. Some are of the degree that Dr. Sprague mentioned, wherein any pain lasting more than half an hour may be listed, at least tentatively, as a myocardial infarction. I do not think that such borderline cases should be definitely so labeled. It may be one of the worst things one can do to a human being and his family in the absence of more definite data. Nevertheless, some physicians are willing to accept all types of borderline evidence as sufficient to make the diagnosis of myocardial infarction. "Do you use anticoagulants for everybody who has had a pain in his chest for half an hour?" I would definitely say "No." One should be more selective. We think that any patient who is sick enough to be hospitalized for myocardial infarction should almost unquestionably receive anticoagulants. If he has typical electrocardiographic changes, substantiated by an elevated white blood cell count, fever, an elevated erythrocyte sedimentation rate, and an increased level of transaminase, this may be considered to constitute definite evidence that there is a change within the muscle of his heart—probably

a myocardial infarct. Such patients should receive anticoagulants, whether at home or in the hospital, if no contraindications exist.

A problem arises when some physicians try to predict whether the myocardial infarction will have a mild or a serious course. Not long ago, we reported 14 patients who, by every criterion that had been suggested, represented mild or good-risk cases. These 14 patients had 18 severe thromboembolic complications. Four of them lost a leg, and 1 of these 4 lost both legs. One lost a toe. Others had severe pulmonary infarctions, and 1 died as a result of thromboembolic complications.

This seems to indicate, as Dr. Ernstene suggested, that we are unable to predict on the first, second, fourth, or even tenth day, whether or not the patient will recover. With every day that passes, the prognosis grows better; but we believe it unjustifiable for the physician to wait until a man has an embolism in his leg, or hemiplegia, before beginning to think he may need anticoagulant therapy. We do not insist that anyone follow our criteria or plan of treatment, but merely state how we handle this situation.

DR. FRIEDBERG: May I say a word?

MODERATOR WRIGHT: Certainly.

DR. FRIEDBERG: I am not referring to mild cases, which may or may not be in the same category, in the sense that there is pain lasting half an hour. I am speaking of patients with unequivocal myocardial infarction by classic standards, but in whom one cannot observe any of the criteria of severity that Russek and others have outlined. In such so-called mild cases, the mortality rate varies from 3 to 5 per cent. The word "mild" should not be used for such cases. A disease that has a mortality rate of 3 per cent is not mild. Many people avoid risks that are much lower than 3 per cent. I like to remember that there was a time when patients with hyperthyroidism in New York, where the mortality rate for thyroidectomy was about 1.8 per cent, went to Boston because somebody there reported a mortality rate of 0.8 per cent. That is not much improvement; nevertheless, I could not get a patient with hyperthyroidism to have a thyroidectomy performed here.

If we could reduce the mortality rate of 3 to 5 per cent to, let us say, 2 or 1 per cent by the use of anticoagulants, then their use would be justifiable. At any rate, I do not believe that the word "mild" should be used for these cases. Every patient with a frank case of acute myocardial infarction carries a substantial risk, and any therapeutic agent that gives promise of reducing the risk should be employed under these circumstances.

MODERATOR WRIGHT: We have discussed the general ideas relating to this subject.

The next question is whether, when one starts using anticoagulants, he should use heparin on the first day. In other words, should we use heparin in order to give the patient *prompt* anticoagulant therapy? Or should we use Tromexan or even the slower-acting drugs like Coumadin and Dicumarol?

Dr. Ernstene, will you take this question?

DR. ERNSTENE: We do not use heparin. We begin our treatment by giving Tromexan at the same time as the initial dose of Dicumarol.

MODERATOR WRIGHT: At New York Hospital, we formerly used heparin very rarely, but have come to use it more often. We carefully select the patients to receive it. We choose especially those who have had premonitory symptoms for several days because, in such instances, we are not certain that they may not have had an infarction a week or ten days previously. In necropsies performed on patients who have had practically no symptoms for ten days preceding a fatal embolic episode, there is frequently evidence in the heart that the infarction probably had been present during the previous ten-day period. Because of this, we tend to use heparin initially. We give 75 mg. subcutaneously or intramuscularly, at twelve-hour intervals for three doses. At the same time, we usually give about 1,200 mg. of Tromexan (ethyl biscoumacetate) and 100 or 200 mg. of Dicumarol. This provides continuous action, as the effects of the first two drugs decline at about the time Dicumarol becomes effective. Some physicians may prefer to use Hedulin (phenylindandione) or any of several other anticoagulants, such as Marcumar, Warfarin or Cumopyran.

Does anyone on the panel believe that one of these has specific advantages over the others, or can we group them and say that knowing how to use one of them is the most important thing. Some act a little faster, and others more slowly, but the long-acting ones no longer present a hazard because their action usually can be terminated within six to twelve hours by the use of vitamin K.

Does anyone wish to take a position favoring one of these specifically?

DR. FRIEDBERG: I have had no experience with Dipaxin and some of the other drugs, but have used Tromexan, Dicumarol and Hedulin. I do not like Tromexan; not that it is ineffective, but it is the hardest to control. In hospital service, it is relatively expensive when used to any great extent on a ward service, or in addition to the other anticoagulants. Between Dicumarol and Hedulin (the two most widely employed), I have the impression that there is a distinct advantage in using Hedulin, as it has the ability to maintain constant prothrombin levels.

When giving successive doses of Dicumarol for example, the effect must be thought of in terms of the dose given forty-eight or seventy-two hours previously. It becomes a little more difficult to regulate dosage in terms of Dicumarol than in terms of a drug that acts more rapidly. Therefore, I sense a distinct advantage in practice when using Hedulin, but I am certainly not dogmatic about it.

DR. SPRAGUE: I agree, in those instances in which I am a little fearful about the laboratory control. I would favor Hedulin in such cases.

MODERATOR WRIGHT: The advantages have been pointed out. I shall mention one disadvantage of Hedulin, particularly for long-term therapy, although that is not what we are talking about now. We tell patients to observe themselves for any evidence of bleeding or bruising, and to watch their urine. Unfortunately, Hedulin often produces an orange-red color in the urine. This is a slight disadvantage, as it may delay recognition of bleeding, and the patients may not get in touch with their physicians as soon as they should.

There is also something to be said for long-term therapy with Dicumarol. We now have patients who travel all over the world while taking Dicumarol. They tell us where they are going, and we give them a list of physicians qualified to check

their prothrombin times and advise them as to dosage. Such a large number of physicians are familiar with the use of Dicumarol, that it is less confusing for the patient who is moving about the world to have Dicumarol therapy regulated in this manner. Even if a physician happens to know more about Marcumar or about Warfarin therapy, he probably started his experience with Dicumarol and can always use it as a point of reference. That constitutes some advantage.

We shall now turn to the question of diet.

Dr. Stamler, we hear a great deal these days about diet, that is, a low-cholesterol, low-fat diet. We want to know how strict this diet should be. Is it really of proved value? Do you believe that, on the basis of present evidence, we should differentiate between saturated and unsaturated fats? In a recently published article it was implied that stress and strain, physical indolence, obesity, luxury living, and tobacco play but a minor role in producing a high death rate from coronary artery disease in persons under 65 years of age compared to a high intake of saturated fats.

Will you discuss this problem?

DR. STAMLER: May I state explicitly that—as Dr. Wright appreciates—the conclusion published was not my statement!

Next, may I clearly define the question under discussion: Our concern at the moment is *not* with the dietary management of *acute* myocardial infarction. Rather, as Dr. Wright indicated, it is with the possible utility of *long-term* dietary treatment. The objective of this therapeusis is the prevention or retardation of recurrent myocardial infarction in patients who have survived one or more previous attacks. The aim is significant prolongation of life in persons—particularly middle-aged individuals—with serious atherosclerotic coronary heart disease.

It must be appreciated that, as yet, no definitive scientific answers can be given to the questions Dr. Wright has posed. They are at present *sub judice*. However, intense research activity has yielded results pointing forcefully in the direction of dietary therapy. This is a brief progress report and interpretative summary of that activity.

Three broad research methodologies—the epidemiologic, the clinico-pathologic, and the animal experimental—have yielded significant data indicating that diet may be useful in the therapy of coronary heart disease. Thus, epidemiologic investigations on populations in different countries have demonstrated a correlation among life-span patterns of diet, plasma cholesterol-beta lipoprotein levels, and the occurrence of atherosclerotic disease.[1] Specifically, whenever the habitual diet is high in total calories, in foods of animal origin (including dairy

[1] For documentation of this conclusion, the reader is referred to the following bibliographic sources: 1) Katz, L. N., and Stamler, J.: Experimental Atherosclerosis. Springfield, Ill., Charles C Thomas, Publisher, 1953; 2) Symposium on Atherosclerosis, National Academy of Sciences. National Research Council Publication 338, Washington, D. C., 1954; 3) Keys, A., and White, P. D., editors: World Trends in Cardiology. I. Cardiovascular Epidemiology. New York, Hoeber-Harper, 1956; 4) Keys, A., editor: Arteriosclerosis—A symposium, *Minnesota Med.* **38:** 731, 829, 1955; 5) Stamler, J.: Current epidemiological, clinical, and laboratory research findings on the etiology of atherosclerosis, *Nebraska M. J.* **41:** 75, 1956.

products), in total fats and saturated fats (animal fats and hydrogenated vegetable fats) and in cholesterol, then plasma cholesterol-beta lipoprotein levels are high and atherosclerotic disease is frequent—in the middle-aged (particularly males) as well as in the elderly. Contrariwise, when the habitual diet is predominantly vegetarian (as in the bulk of the populations of Asia, Africa and Latin America) and is low in total calories, total fats, animal fats, and cholesterol then plasma cholesterol-beta lipoprotein levels tend to be low (cholesterol usually well under 200 milligrams per 100 ml.) and atherosclerosis is rare clinically and morphologically. Incidentally, these findings strongly suggest that the accepted United States standards for normal concentrations of plasma cholesterol are set far too high, if the criterion be the optimal level for freedom from atherosclerotic disease over the life span.

These epidemiologic conclusions are based on remarkably consistent data from vital statistics, insurance company records, necropsy surveys, hospital admission records, outpatient clinic records, and representative medical surveys. Moreover studies on social-class trends, on the effects of migration and on the influences of wartime indicate that the observed correlations are not genetic, racial or ethnic in origin; nor are they byproducts of climate or geography. Diet is almost certainly the decisive causative factor.

Clinical investigations have demonstrated clearly that myocardial infarction in middle-aged persons tends to be associated with a hypercholesterolemic state. They have also shown that certain diseases—hypothyroidism, essential familial xanthomatosis, diabetes mellitus and nephrosis—characterized by prolonged periods of hypercholesterolemic hyperlipemia, tend to be complicated inordinately by premature, severe atherosclerotic disease. Further, clinical studies have conclusively demonstrated that plasma cholesterol levels are highly amenable to dietary influence. Thus, simple overeating with resultant gain in weight is associated with an increase in the concentration of plasma cholesterol. A similar response is observed when the percentage of total calories from animal fat is increased in an isocaloric diet (with weight remaining stationary). Contrariwise, weight reduction is associated in most individuals with a significant fall in the plasma cholesterol level. Cholesterolemia is also decreased following ingestion of low-fat, low-cholesterol, isocaloric diets (without weight alterations). Similarly, the plasma cholesterol level is lowered when unsaturated vegetable oils are substituted for saturated animal fats in an isocaloric diet.

Animal experiments have also yielded significant data lending support to the concept of a basic interrelation between diet, plasma cholesterol-beta lipoprotein levels, and atherogenesis. To see the problem in proper perspective, it must be appreciated that experimental atherosclerosis as a research discipline has a history and a pre-history—the dividing line being about the year 1910. Until that time, many unsuccessful attempts had been made to produce the lesion of human atherosclerosis in laboratory animals. During the years 1908 to 1912, Anitschkow, Ignatowski and Chalatow showed that in rabbits fed animal tissues, gross hypercholesterolemic hyperlipemia and aortic atherosclerosis developed. In successive experiments, they soon demonstrated that the decisive atherogenic factor was dietary lipid, *i.e.*, cholesterol and neutral fat.

In recent years, hypercholesterolemia and atherosclerosis have been induced successfully in one after another of the major laboratory species, herbivorous, omnivorous and carnivorous. Invariably, dietary alteration is a prerequisite—a high-fat, high-cholesterol ration being needed under most circumstances. In the dog, hypercholesterolemia and resultant atherogenesis have been induced by feeding a high-fat, high-cholesterol diet and rendering the animal hypothyroid; and in the monkey and the rat, by feeding a diet high in fat and cholesterol and deficient in the sulfhydryl-containing amino acid, methionine.

Herbivorous rabbits and omnivorous chicks have been made atherosclerotic without the induction of massive hypercholesterolemia and organ lipidosis, by feeding small amounts of cholesterol and fat over long periods of time. The pattern of diet in these experiments, as well as the diet-induced hypercholesterolemia, closely resembled the pattern in middle-aged Americans with atherosclerotic disease.

These epidemiologic, clinico-pathologic and animal experimental facts forcefully validate the dietary-metabolic theory of atherogenesis. They strongly support the conclusion that the lifespan pattern of diet is the decisive influence making for extensive sustained hypercholesterolemia and epidemic coronary disease in our country.[2] They demonstrably point toward modification of diet as a key prophylactic and therapeutic measure to bridle this disease.

A new dimension has been added to our understanding of nutritional-metabolic relationships in atherogenesis as a result of the findings recently reported from a long-term epidemiologic study at Framingham, Massachusetts. This investigation has unequivocally demonstrated a several-fold increase in the risk of clinical coronary heart disease in middle-aged males with obesity, hypercholesterolemia (260 milligrams per 100 ml. or greater), and/or elevated blood pressure (160/95 or greater). In this study, the large population—originally free of clinical coronary heart disease—was divided into two groups. In one group, the values for body weight, blood pressure and plasma cholesterol level were normal; in the other group, two or three of these values were elevated. Over a four-year period, the occurrence rate of myocardial infarction was fourteen times as great

[2] This theory does not deny or overlook the possible role of other factors in atherogenesis and coronary disease, *e.g.*, genetics, heredity, endocrine dysfunction, stress and strain, smoking, infections, hypertension, and physical activity. It merely emphasizes that a certain type of habitual diet is a prerequisite for significant atherogenesis and coronary heart disease in a given population. Given this atherogenic diet as the pivotal influence, the other factors then come into play to retard or accelerate the disease process in particular individuals and strata of the population. This is the sole interpretation which fits the complex of facts concerning the multifaceted factors apparently involved in the causation of coronary disease.

Similarly, the dietary-metabolic theory focuses on the problem of the causation of the pathologic lesion—the atherosclerotic plaque—which is of decisive (but not exclusive) importance for the development of clinical coronary heart disease. This theory does not deal with the problem of factors which precipitate the acute clinical episode (*e.g.*, sudden collapse, with or without coronary thrombosis and myocardial infarction). Some recent data suggest that high-fat diets may increase the risk of occlusion by enhancing blood coagulability. Be this as it may, the causation of acute episodes is a highly complex problem—but a problem secondary (in time and consequence) to that of atherogenesis.

in the latter group (Dawber, T.; Moore, F., and Mann, G.: *Am. J. Pub. Health* **47** (Part 2): 4, 1957). Obesity, hypertension and hypercholesterolemia in combination increased the risk of coronary heart disease in middle-aged males more than tenfold!

When it is appreciated that these defects are amenable to influence by dietary and other measures, the fundamental rationale for attempting to treat coronary heart disease by dietary means immediately becomes clear. Permit me for a moment to indulge in a scientific speculation, based on an extrapolation from the finding in the Framingham Heart Study. Assume that by dietary and other feasible hygienic-medical means obesity, hypercholesterolemia, and/or hypertension are corrected in a sizable group of middle-aged American males. Might we not anticipate—extrapolating from the Framingham data—a significant (several-fold) lowering of the risk of myocardial infarction?

The definitive answer to this critical question is not yet forthcoming; it awaits five or ten years of additional experimental epidemiologic research. However, life insurance studies have demonstrated that maintained weight reduction eliminates the inordinate risk incurred by obese Americans of dying from cardiovascular-renal diseases, including coronary heart disease.

A decisive large-scale, long-term *prophylactic* study of the type described remains to be performed. Similarly, a carefully controlled *therapeutic* study remains to be accomplished for evaluation of the efficacy of diet in the treatment of patients in whom manifest clinical coronary heart disease has already developed.

In the final analysis, there is only one scientific basis for concluding definitively that diet is useful in the therapy of coronary heart disease. Valid proof can be obtained only from a study conducted over a period of many years demonstrating that such a regimen significantly prolongs life expectancy beyond that anticipated without dietary treatment.[3] Findings with respect to such factors as plasma cholesterol-lipoprotein levels, eyegrounds, electrocardiographic and ballistocardiographic patterns, or anginal symptoms do not suffice.

To date, 2 reports have appeared in the literature on the long-term effects of low-fat low-cholesterol diets (25 to 50 grams of fat per day) in the therapy of clinical coronary heart disease. Both of these reports claim to have demonstrated definite therapeutic results, that is, significant prolongation of life resulting from significant decrease in the incidence of fatal recurrent myocardial infarction. Unfortunately, one of the studies (Morrison, L. M.: *J.A.M.A.* **159:** 1425, 1955),

[3] The problems involved in properly designing such long-term therapeutic evaluations have been discussed at length in a recent report (Stamler, J.; Pick, R., and Katz, L. N.: Experiences in assessing estrogen anti-atherogenesis in the chick, the rabbit, and man, *Ann. New York Acad. Sc.* **64:** 596, 1956). With respect to dietary therapy, the following problems of design need further clarification: Precisely what diet should be used? Specifically, what is the minimal alteration in diet—retaining the virtues of simplicity, convenience, economy, practicability, familiarity, acceptability, palatability, enjoyability, satiety—that will accomplish the mission? What are interim criteria of efficacy? Are serum cholesterol levels adequate for this purpose? How is adherence to be evaluated? These are cardinal problems for the research worker in this area.

conducted over a period of eight years, does not appear to be properly designed for adequate control, insofar as one can judge from the published report. The other (Lyon, T. P.; Yankley, A.; Gofman, J. W., and Strisower, B.: *California Med.* **84:** 325, 1956), conducted over a period of five years, is apparently well controlled. However, the report is brief and sketchy and appears to be a preliminary one; hence, judgment must be reserved concerning its conclusions, pending a presentation of the data in full. [4]

This, then, is the present status of the problem posed by Dr. Wright. In brief summary, a vast array of evidence—epidemiologic, clinico-pathologic, and animal experimental—has accumulated, strongly indicating that an alteration in dietetics is likely to be highly efficacious in the prophylaxis and therapeusis of coronary heart disease. However, definitive and final proof is not yet forthcoming. This will require several more years of precise and intensive research.

Given this situation, what should be the approach of the practicing physician? This should not be too difficult a question to answer. If events are permitted to take their present course, it is clear what will continue to happen to middle-aged men who at present are clinically well, and to those already stricken. Epidemic coronary heart disease will continue to plague us unabatedly. A *laissez faire* attitude on the part of physicians towards diet, obesity, hypercholesterolemia and high blood pressure will result only in the perpetuation and aggravation of the already grim situation. Hence, the burden of proof seems to rest inevitably with those in the profession who say in effect, "We know too little as yet to do anything." That approach is untenable, particularly since current proposals for dietary-hygienic intervention are patterned on simple, safe, and sound lines that in any case can do no harm. Given the known outcome without intervention, and the very good possibility of reducing risk and improving prognosis through reasonable practicable dietary-hygienic measures, the profession's responsibility to act seems compelling.

MODERATOR WRIGHT: Dr. Stamler, I know we all have questions, and I should like to ask one. You have used data based on persons who had an elevated blood cholesterol level. If you were to take 1,000 persons with myocardial infarction who did not have an elevated blood cholesterol level, would there be any evidence that a very low cholesterol diet, which might make them fairly miserable and unhappy about not having their eggs for breakfast, would affect their longevity?

DR. STAMLER: In answering this question, it is first necessary to emphasize an essential point made abundantly clear by our own data, as well as by the findings of the Framingham Heart Study, the Cooperative Lipoprotein Study, and other investigations. Clinical coronary heart disease is rare in middle age in normocholesterolemic persons (cholesterol level below 225 or 200 milligrams per 100 ml.). It would be most difficult to gather a case series of 1,000 normocholes-

[4] The status of other possible long-term practicable therapies is essentially similar. Thus, the results of laboratory and clinical studies have suggested that long-term treatment with anticoagulants, plant sterols, or estrogens may be useful in the treatment of clinical coronary heart disease. However, no definitive data demonstrating their efficacy are as yet available from controlled studies.

terolemic persons with myocardial infarction. This is borne out by our own experience since 1952, in accumulating a case series of over 200 men under age 50 with myocardial infarction (for assessment of the possible therapeutic efficacy of long-term estrogen therapy). Very few of them exhibit plasma cholesterol levels below 200 or 225 milligrams per 100 ml. Permit me to re-emphasize that the risk of getting this disease is remarkably lowered in middle-aged American males when they are free of obesity, hypertension, and hypercholesterolemia; and that normocholesterolemic Bantu, Nigerians, Guatemalans, and Japanese are highly resistant to the disease. May I also re-emphasize the point about acceptable normal standards for plasma cholesterol concentration. In view of the latest data, hitherto accepted American standards need revision downward. Certainly, levels frequently observed in our middle-aged population (in the range 230–280 milligrams per 100 ml. and above) are not optimal, in terms of avoidance of myocardial infarction in persons over the age of 40 to 65. A valid upper limit for the normal range would seem to be no higher than 225 milligrams per 100 ml.

Now, to deal with the question: Should normocholesterolemic males with myocardial infarction still receive dietary therapy? In the light of the foregoing, this question is almost rhetorical—at least insofar as the focus is on treatment of middle-aged patients. Practically, the question refers to only a small group of patients. The majority of middle-aged males with this disease, as seen by the physician, exhibit slightly, moderately or markedly elevated serum cholesterol levels. Undoubtedly, they are candidates for dietary therapy. As to the normocholesterolemic group, my inclination is to take reasonable steps to correct their dietary aberrations as well.

MODERATOR WRIGHT: Dr. Stamler are you on a low-cholesterol, low-fat diet?

DR. STAMLER: I have modified my diet. It now is so constituted that no more than 20 to 25 per cent of total calories come from fat. This is accomplished, if I may elaborate, in the following simple way: First, by avoiding the usual type of American breakfast, two eggs fried or scrambled in butter, fried bacon or ham or sausage, toast soaked with butter, and coffee laden with cream and sugar. I avoid cream on cereals, and bypass wheat cakes smothered in empty calories[5] from syrup and lipid from butter.

For lunch and dinner, meats, poultry and fish are broiled, boiled, pressure-cooked or roasted and the fat drippings are discarded, not mixed into a thick gravy. There is no deep-fat frying, and only occasional frying (with vegetable oils). Salads are eaten with lemon dressing or with a modest amount of French or garlic dressing made with unsaturated oils. Vegetables are eaten without added butter or margarine. Fresh and stewed fruits predominate for dessert, rather than pie, cake or ice cream. Table salt and sugar are avoided, as are empty calorie foods in general. Whole-grain products rate high. All these steps are simple and practicable. They involve moderate—not drastic—changes in current American eating habits. They ensure a highly nutritious, well balanced diet

[5] Empty calorie foods are highly processed foods replete with calories but low in essential nutrients. Examples of such foods are refined sugar and sugar products, hydrogenated fats, unenriched white flour products and alcohol.

containing a high ratio of essential nutrients to calories, and fully adequate amounts of proteins, vitamins, minerals and bulk. They permit a wide range of foods and recipes, calculated to appeal to the gustatory proclivities of even exacting gourmets (*cf.* "Low Fat Cookery" by E. S. Stead and G. K. Warren. New York, Blakiston-McGraw Hill, 1956). These simple dietary measures permit satiety without excess calories. They are effective for combating obesity. They assure correction of the detrimental excesses and imbalances in the contemporary American diet.

MODERATOR WRIGHT: Do you take corn oil, and do you eat much fish?

DR. STAMLER: I enjoy sea food, and eat it fairly frequently—prepared according to the foregoing precepts. As to corn oil, may I first put forward a general proposition: If there is a deficiency of unsaturated and essential fatty acids in the American diet, it can only be a secondary relative deficiency—a deficiency of imbalance, consequent upon dietary excesses. Thus, all experiments on essential fatty acid (EFA) deficiency in animals show that this condition can be induced only with practically complete removal of fat from the diet. Burr and Burr demonstrated this many years ago. The American diet is *not* such an EFA-deficient ration; quite the contrary. Thus, butter and hydrogenated vegetable fats contain 2 to 10 per cent essential fatty acids (chiefly linoleic acid). Milk and milk products have a significant EFA content. Animal fat in general is composed of about 9 per cent essential fatty acids. The average American, therefore, ingests large amounts of essential fatty acids every day, irrespective of his intake of vegetable oil. He actually consumes much more EFA than most other peoples—much more than any estimated minimum daily requirement. If he is actually suffering from a metabolic deficiency of EFA, it cannot be the resultant of primary lack of dietary EFA *per se*. It can only be a relative deficiency, secondary to the excessive intake of saturated fats, refined carbohydrates and/or total calories—that is, an *imbalance*, with inadequacy of EFA due to a large need stemming from other dietary aberrations. As a matter of fact, there is good experimental evidence to show that the metabolic need for essential fatty acids in animals is proportional to the intake of total calories, total saturated fats, and cholesterol. An amount of EFA which may be adequate in a certain diet becomes inadequate when more saturated fat, calories and cholesterol are added. This, by the way, is true for several essential nutrients, for example, vitamins, methionine and other amino acids.

This argument is not a mere abstract mental exercise. It has great practical import. Thus, if it be correct, the corollary is that the imbalances in the American diet cannot be rectified by *adding* quantities of corn oil to our present diet, without other modifications. Such an approach is impractical, unpalatable and unwise, if for no other reason than the fact that it would further increase the intake of fat, absolutely and relatively, as well as the total caloric intake, with resultant increased risk of obesity. It is further unwarranted, since few good data are as yet available indicating that *addition* of corn oil to mixed diets consistently lowers plasma cholesterol levels. A more sound approach is to correct the imbalances in the American diet—first of all, by reducing the excesses of total

calories, total fat, saturated fat, cholesterol and empty calories, and secondly, by adding essential nutrients of all types (*e.g.*, EFA, vitamins) as indicated in the foregoing dietary recommendations.

MODERATOR WRIGHT: Dr. Friedberg, how rigid a diet do you prescribe for patients who have had one myocardial infarction?

DR. FRIEDBERG: I try to follow the rules just stated. I do it, though, with the realization that although all the factors mentioned are associated with a higher incidence of myocardial infarction, we still do not know whether the reduction of obesity, high blood pressure, and hypercholesterolemia will necessarily reduce myocardial infarction or diminish mortality. However, I do advocate reduction of the intake of fats and total calories.

MODERATOR WRIGHT: To protect the life of the individual?

DR. FRIEDBERG: Yes.

MODERATOR WRIGHT: Dr. Ernstene?

DR. ERNSTENE: I do much the same, but with particular emphasis on the importance of reducing the amount of fat in the diet, and reducing cholesterol only to the point of avoiding an excess intake.

MODERATOR WRIGHT: A few questions have been submitted from the floor.

Does myocardial infarction ever occur from a subintimal hemorrhage? If so, how does an anticoagulant affect this condition? This was feared and so it was investigated in the original study. We found among cases at necropsy that subintimal hemorrhage could have contributed to death in only 3 per cent, although all pathologists (16 were involved) were asked to study the coronary arteries carefully with this in mind. I am sure that the necropsies were performed more carefully than usual; yet, subintimal hemorrhages were important in only 3 per cent. Some occurred in the controls, and some in the treated patieuts. The numbers were too small for accurate evaluation.

QUESTION TO DR. ERNSTENE: *Would you give an anticoagulant to a patient with a severe myocardial infarct who has a history of roentgenographically proved ulcer?*

Yes, I would, provided the patient was not bleeding.

QUESTION TO MODERATOR WRIGHT: *What are the mortality statistics for myocardial infarction in shock?*

We must consider the definition of shock. The statistics that have been issued vary from 40 to 85 per cent, depending upon the series under consideration, and the definition of shock used.

QUESTION TO DR. FRIEDBERG: *How do you treat severe shock in myocardial infarction? Do you use Levophed or something like that?*

DR. FRIEDBERG: I do.

MODERATOR WRIGHT: Dr. Ernstene, do you agree that Levophed is useful for the treatment of shock following myocardial infarction?

DR. ERNSTENE: Yes.

QUESTION TO MODERATOR WRIGHT: *What is your favorite anticoagulant?* We have answered this problem. My present favorite anticoagulant is Dicumarol, after having tried almost everything on the market, and for the reasons that I

outlined. We also use Marcumar. If Marcumar were made in this country, we might use it more frequently. The other anticoagulants are used with about equal frequency. Have you any preference, Dr. Ernstene?

DR. ERNSTENE: Our preference is for Dicumarol.

MODERATOR WRIGHT: Here is a question for you, Dr. Friedberg. *Is the diagnosis of coronary artery disease justified on the basis of a Q3 and QAVF that satisfy criteria as to size and depth, if seen after an infarction? If seen when there is no history of chest pain or cardiac symptoms of any kind?*

DR. FRIEDBERG: This is very interesting. In general, I would stress that the diagnosis of acute myocardial infarction, insofar as possible, should be made on the basis of the correlation of the clinical picture with the electrocardiogram, even though sometimes the electrocardiogram is so typical of an infarct that you can be virtually certain on that basis alone. However, in a patient who has had an infarct in the past, and particularly when there is a posterior-wall infarction (the type of case manifesting Q3 and QAVF), a diagnosis of fresh infarction is not justified, especially in the absence of chest pain or other cardiac symptoms. It was said at one time that, when a Q wave is present in lead 3 and not in AVF it may be regarded as being caused by the electrical position of the heart, whereas when a Q wave is present in both AVF and 3 it more likely indicates a true posterior-wall diaphragmatic infarction. This statement has some statistical support, but I have seen many instances of Q waves in the electrocardiographic leads in patients who have not had myocardial infarction.

MODERATOR WRIGHT: Thank you. This concludes the panel discussion.

EXTENDED SYMPATHECTOMY IN THE TREATMENT OF CHRONIC ARTHRITIS

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Treatment of the patient with advanced chronic arthritis, not infrequently, presents a continuing problem to the attending physician. The recent additions to the rheumatologist's armamentarium, notably the corticosteroids, have their limitations, in that their beneficial effects are temporary and they induce side-reactions when employed over a protracted period. In the arthritic patient, unresponsive to medical and physiotherapeutic regimens, resort must be made at times to surgery for relief of intractable pain in the joints.

Among the procedures suggested have been synovectomy, tenotomy, arthrodesis, arthroplasty, osteotomy, and various denervation procedures. The latter usually take the form of spinothalamic chordotomy and, more frequently, peripheral neurectomy. Chordotomy in many cases yields disappointing results in the relief of pain, and on occasion gives rise to distressing bladder and bowel disturbances. The more common neurectomies are designed to divide the peripheral somatic nerves supplying the joints affected. White, Smithwick and Simeone (1) in their authoritative monograph assert that all evidence points to the mediation of articular pain through the peripheral spinal somatic nerves. The surgical approaches to these nerves have been standardized for purposes of neurectomy for the relief of articular pain (2). Unfortunately, peripheral neurectomy has been disappointing when employed for this purpose (3). Moreover, severance of a peripheral nerve produces varying degrees of motor and sensory disability because of interference with its muscular and cutaneous distributions (4).

Sympathectomy has been employed cursorily in the past for the relief of arthralgia. Rowntree and Adson (5) reported in 1927 a series of young patients with rheumatoid arthritis and associated vascular insufficiency who seemingly benefited from sympathetic ganglionectomy. Flothow (6) in 1930, Leriche and Jung (7) in 1933, and Young (8) in 1936 also reported relief of articular pain in small series of patients with rheumatoid arthritis. White and his co-workers (1), however, were not impressed favorably by the results of sympathectomy in 5 patients with rheumatoid arthritis. The conflicting reports of these investigators and the remarkable absence of follow-up observations by those who were originally enthusiastic, suggest that there had been either incomplete denervation or regeneration of the afferent sympathetic fibers (9–11). Residual and recurrent sympathetic activity have been demonstrated repeatedly in patients who have undergone conventional lumbar sympathetic ganglionectomy (9–11). Therefore, lumbar sympathectomy should be anatomically complete in order to effect significant and lasting relief in the syndromes in which the operative procedure

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is indicated. Kuntz (12) demonstrated the existence of accessory ganglia in the lumbar segments. The rami communicantes of the accessory ganglia do not enter the paravertebral lumbar sympathetic chains. Located on the rami of the sympathetic chain and also on the anterior lumbar nerve roots, the accessory ganglia are distinct from the usual sympathetic ganglia and probably function independently (12). Decussating sympathetic fibers, originating in contralateral lumbar sympathetic ganglia have also been described (13, 14).

EXTENDED LUMBAR SYMPATHECTOMY

A technique of so-called extended lumbar sympathectomy (15) has been employed by the author to encompass the foregoing anatomic variations in the lumbar sympathetic system. This procedure consists of division of the sympathetic chain at or immediately distal to the first lumbar sympathetic ganglion in the crus intermedius of the diaphragm, with removal of ganglia 2, 3 and 4 and the intervening trunk, as well as division of the rami entering the chain as far as possible laterally in the psoas muscle border so as to include the accessory ganglia (16). The final step in extended lumbar sympathectomy consists of denudation of the vertebral periosteum of decussating and residual unorganized longitudinal fibers by cross-hatch incisions over the antero-lateral aspect of the lumbar vertebral bodies, after mobilization and retraction of the inferior vena cava on the right and the abdominal aorta on the left. In the event of a right sided procedure, the inferior vena cava is mobilized after dura clip occlusion and division of the lumbar veins coursing anterior to the sympathetic chain. Dura clips are applied to the proximal and distal ends of the resected sympathetic trunk, to ensure against regeneration. Periosteal bleeding following vertebral scarification and denudation is controlled by topical application of gelfoam pledgets and by permitting the intact posterior parietal peritoneum to fall into the lumbar paravertebral gutter. In this series, extended lumbar sympathectomy was carried out retroperitoneally through an oblique muscle-splitting incision extending from the tip of the eleventh rib antero-inferiorly toward the lateral border of the rectus abdominis. General inhalation anesthesia was used in all cases.

In the present communication, case histories are presented on 7 patients with advanced chronic arthritis and intractable pain in the hip or knee joints, who received the benefits of extended lumbar sympathectomy.

CASE HISTORIES

Case 1

L. C., a 63-year-old white, married woman had had progressive rheumatoid arthritis since the age of 45. Early in the disease the joints of the hands and upper and lower extremities were involved in the arthritic process, with attendant limitation of motion and pain. There had been periodic redness and swelling of these joints in the three years before admission, but there had been more inflammatory activity in the right knee than in the other joints. In 1953 and again in 1954 courses of cortisone were administered, and there had been temporary symptomatic relief; however, the pain and limitation of motion promptly returned on cessation of therapy. For the two-year period prior to the last admission to the

hospital, she had been unable to walk by herself, and had required a walker or wheelchair to get about the house. For the same period she had been unable to turn on her side in bed without assistance because of the immobility of the hips, knees and ankles. These joints had been the sites of more or less continuous pain at rest, with exacerbation of pain on attempted active or passive motion or with the advent of inclement weather. The pain had necessitated the use of approximately 30 grains of aspirin and 1 to 2 grains of codeine daily over the previous fifteen years. Ulceration of the skin over the distal thirds of both legs had been noted since the initial course of cortisone therapy in November 1953.

The patient was admitted to Grasslands Hospital for the first time in June 1954, for the application of skin grafts to the ulcerative lesions of the legs. Examination at that time revealed the presence of hypertensive cardiovascular disease in addition to far-advanced rheumatoid arthritis with complete limitation of motion at the hips, knees and ankles. Pinch grafts were applied to the ulcers over the right leg on June 7, September 7, and December 14, 1954, but sloughing of the grafts followed on each occasion. Split-thickness dermatome grafts were applied to the granulating ulcerations over the left leg on September 7, 1954, with a similar lack of success.

She was admitted to Grasslands Hospital for the fourth time on January 7, 1955, and examination revealed multiple granulating ulcerations, 1 to 2 inches in diameter, over both legs in the distal thirds. There was complete limitation of motion at the hips, knees, ankles, elbows and wrists (Fig. 1). Marked arthritic deformities were present in the metacarpophalangeal, metatarsophalangeal and interphalangeal joints. The patient was confined to bed, in which she lay with elbows, hips and knees in a position of partial flexion. She complained of pain in all these joints, the right knee being the most painful. Her feet and legs were cool and pale; popliteal, posterior tibial and dorsalis pedis pulses were present bilaterally. The erythrocyte sedimentation rate on January 10 was 26 mm. per hour (corrected). On January 17 a right lumbar sympathetic block, employing 1 per cent procaine, induced a rise in temperature of some 8 degrees F. in the right foot, with simultaneous diminution of pain in the right knee and ankle.

On January 19 an extended right lumbar sympathectomy encompassing the second, third and fourth lumbar ganglia was carried out by the retroperitoneal approach. On the first

FIGURE 1

postoperative day the patient stated that she was free of pain in the right hip, knee and ankle; also that the right lower extremity was warm and dry, and that she could move it actively without the usual pain. The ulcerations over the right leg became epithelialized within ten days after surgery. On January 31 an extended sympathectomy was carried out in the left lumbar area with similarly gratifying results.

In January 1957, two years after extended sympathectomy, the patient was ambulatory without support. She stated that she could walk and stand without pain. Analgesic drugs had not been employed in the previous twenty-four months. The ulcerations were completely epithelialized; both feet and legs were warm and dry. The right hip had 45 degrees of flexion and 30 degrees of abduction; the right knee had 90 degrees of flexion; the right ankle had a 30-degree range of motion. The left hip had 45 degrees of flexion and 30 degrees of abduction, the left knee had 90 degrees of flexion, and the left ankle had a 30-degree range of motion. The patient offered the observation that the mobility of the joints was increasing progressively, as she had been more active since leaving the hospital.

Case 2

D. G. (a patient of Dr. Harold Nottley) was a 72-year-old woman who was seen for the first time in April 1955. She had had a swollen, painful right knee for the previous six weeks. She stated that she had had periodic pain and swelling in the right knee over the course of the previous forty years. Walking and weight-bearing had not been possible because of severe pain, for the previous four weeks. Roentgenograms of the right knee revealed marked hypertrophic changes with osteophyte formation and thinning of the joint cartilage, indicating rheumatoid arthritis with superimposed osteoarthritic change (Fig. 2). On examination, an exquisitely tender, swollen right knee was noted. The patient, complaining of pain in the part when it was at rest, refused to permit passive motion at the knee joint. There was 10 degrees of active flexion. The patient declined further medication, having run the gamut of drugs including phenylbutazone, cortisone, and metacortandracin.

On April 19, 1955, at St. Agnes Hospital, an extended lumbar sympathectomy was carried out on the right side. On fully recovering from anesthesia, the patient remarked on the absence of pain in the right knee and demonstrated 60 degrees of active flexion. On the fifth

FIGURE 2

postoperative day she walked and stood without pain. The immediate postoperative period was marked by the development of wound infection, which responded to local incision and drainage. Two weeks after sympathetic denervation, the patient was completely ambulatory without pain, and the swelling of the joint had subsided. When examined in December 1956, eight months after sympathectomy, she could stand for protracted periods and could walk without pain except in inclement weather, at which time she noted some aching distress in the joint with associated stiffness. Upon examination at this time, there was no evidence of effusion or periarticular swelling; there was 110 degrees of active flexion.

Case 3

J. G., a 78-year-old man, was first seen in December 1955. He had a thirteen-year history of progressively severe pain in the right hip. For the six months before admission the pain in the right hip at rest was severe and did not respond to analgesics or physiotherapy. Examination revealed an elderly male with some senile personality changes, who was confined to bed and could neither stand nor walk. He complained of severe pain in the right hip and groin at rest; there was 45 degrees of active flexion at the joint. X-ray examination showed changes in the right hip indicative of malum coxae senilis with decrease in the joint space and osteophyte formation (Fig. 3).

On December 27, 1955, an extended right lumbar sympathectomy was performed; on the first postoperative day the patient remarked on the absence of pain in the right hip, both at rest and on weight-bearing. On the third postoperative day, the patient had no complaints and the right hip exhibited 110 degrees of active flexion. On December 1, 1956, twelve months after the sympathectomy, this patient was free of pain in the right hip joint; there was 130 degrees of active painless flexion. He could walk freely without support.

Case 4

E. B. was a 62-year-old woman who, on admission in February 1956, had a two-year history of pain, stiffness, and swelling in the right knee. The pain was present at rest and

FIGURE 3

became more severe on weight-bearing. Examination revealed a tender, swollen right knee that was 2 inches larger in circumference than the asymptomatic left knee, and had 45 degrees of active flexion. X-ray examination on February 20, 1956, showed moderate osteoarthritis with squaring of the articular margins, shortening of the tibial spine, and osteophyte formation (Fig. 4).

On February 21, 1956, an extended right lumbar sympathectomy was performed uneventfully. On the first postoperative day, there was no pain in the right knee at rest and 120 degrees of active flexion was elicited. On the fourth postoperative day, there was no pain in the joint either at rest or on weight-bearing; the right knee measured 2 inches less in diameter than the left. On December 27, 1956, ten months after sympathectomy, the patient was free of pain at rest and on walking; the right knee had 150 degrees of active flexion and measured 2 inches less in circumference than the left. Crepitus could be elicited in the right knee joint by active and passive flexion.

Case 5

E. A., a 56-year-old white woman, was first seen in March 1956. She had a history of progressive rheumatoid arthritis involving all joints of the extremities; the onset of the disease was in 1949. From November 1955 to the time of admission to the hospital she had been unable to stand or walk because of pain in the right knee. In the course of the disease, she had been treated with intensive physiotherapy, salicylates, phenylbutazone, and corticosteroids without significant relief. Examination revealed a thin, middle-aged woman who was bedridden. She had obvious advanced rheumatoid arthritic deformities of the joints of all four extremities. The right leg was the site of multiple superficial ulcers over the distal third. The skin of the right leg was cold and moist. The right knee had 80 degrees of active flexion; the right hip, 45 degrees of active flexion. X-ray examination of both these joints showed changes consistent with advanced rheumatoid arthritis (Fig. 5). On March 14, 1956, the white blood cell count was 3,000 per cu. mm. and the erythrocyte sedimentation rate was 5 mm. per hour (corrected).

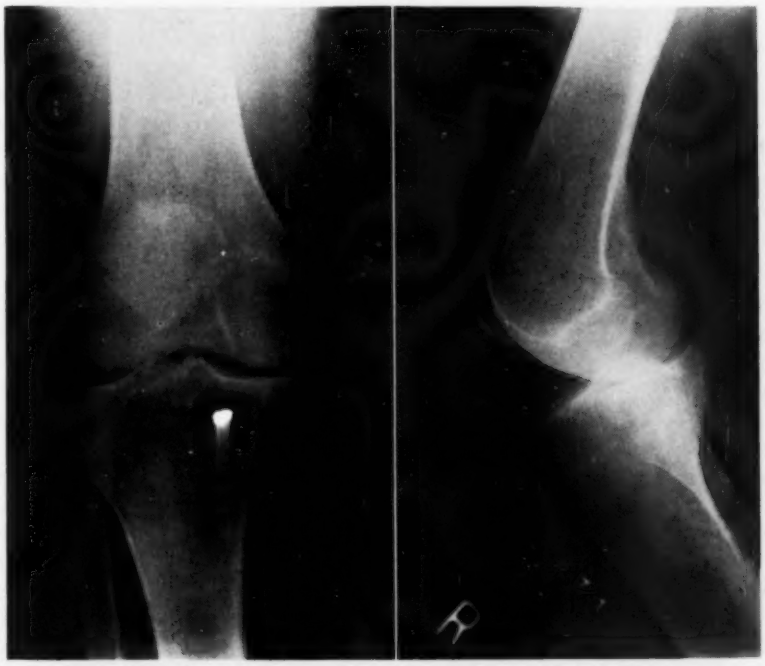

FIGURE 4

FIGURE 5

On March 16, 1956, a right lumbar sympathetic nerve block was performed, using 1 per cent procaine. Transient relief of pain in the right hip and knee was noted, with associated generalized warmth and relaxation throughout the right lower extremity. On March 26, 1956, an extended right lumbar sympathectomy was carried out by the retroperitoneal approach; it encompassed the paravertebral sympathetic trunk from a point proximal to the second lumbar ganglion to, and including, the fourth ganglion. On the first postoperative day the patient was free of pain in the right hip and knee; the right leg was warm and dry. On the third postoperative day, the patient could stand on the right leg and the ulcerations over the lower leg were dry. On December 22, 1956, nine months after surgery, the patient had no pain at rest or on weight-bearing in the right hip or knee, and the ulcerations were completely epithelialized. The right knee had 100 degrees of painless active flexion; the right hip, 90 degrees of active flexion.

Case 6

J. R., a 49-year-old white woman had a six-year history of painful swelling of the right knee. She had noted the onset of painful swelling of wrists, fingers and right knee in 1950, at the age of 43. She had received intensive treatment with salicylates, cortisone, ACTH, and hydrocortisone but had obtained only partial and fleeting relief. A secondary tonsillectomy had been resorted to in 1952, to no avail. The right knee had been the site of painful swelling and stiffness, more or less continuously, since 1950. Examination revealed spindling of all fingers. The right knee was red, tender, and warm; flexion (active and passive) was confined to 45 degrees. On May 3, 1956, the white blood cell count was 4,800 per cu. mm. and the erythrocyte sedimentation rate was 29 mm. per hour (corrected). X-ray examination of the knee on May 3, 1956, showed marked narrowing of the joint space with destruction of the cartilage. There was eburnation of the adjacent articular surfaces with productive change along the margins of the medial condyle of femur and tibia, and some periarticular demineralization. The x-ray findings were indicative of rheumatoid arthritis (Fig. 6).

On May 8, 1956, the right lumbar sympathetic chain was exposed and found to be covered

in its proximal extent by anomalous multiple large lumbar veins. It was felt that these vessels could not be safely ligated and divided so as to expose the underlying sympathetic trunk. The third and fourth sympathetic ganglia alone were removed, with some difficulty. The second lumbar ganglion and proximal sympathetic chain were left behind the anomalous lumbar veins draining into the inferior vena cava. The periosteum over the third and fourth lumbar vertebrae was scarified. On the first postoperative day the patient had no pain in the right knee at rest, although weight-bearing was painful. In the first postoperative month there was a gradual return of pain at rest; by August 1956 the patient felt that the pain in the right knee was essentially the same as it had been prior to surgery. On examination in August 1956 the right knee was tender, painful, and had 80 degrees of active flexion.

Case 7

E. J., a 75-year-old white widow actively engaged as a medical office secretary, had an eight-month history of pain and swelling in the right knee. The pain, moderate at best, became more severe on standing and walking and prevented her from carrying out her secretarial duties. The right knee, following trauma, first became painful and swollen in 1925 and responded at that time to injections of autogenous vaccine prepared from stool. The knee was asymptomatic until January 1956, at which time a progressively painful

FIGURE 6

FIGURE 7

swelling was noted again. There was no significant response to the corticosteroid drugs administered either systemically or by the intra-articular route. X-ray examination of the right knee on June 26, 1956, revealed moderately advanced hypertrophic osteoarthritis with squaring of the articular margins, sharpening of the tibial spines, and production of osteophytes. There was also moderate narrowing of the joint space, apparently due to degenerative changes. The x-ray findings indicated moderately advanced osteoarthritis of the right knee with considerable degeneration of the disc and narrowing of the joint space (Fig. 7). Examination revealed a painful, tender, swollen right knee with 60 degrees of active flexion.

On August 20, 1956, a right extended lumbar sympathectomy was carried out. On the first postoperative day there was no pain at rest and the patient could stand and walk free of pain in the right knee; there was 110 degrees of active flexion. When last examined on December 18, 1956, four months after sympathectomy, the patient was free of pain at rest and could stand and walk without pain; the right knee had 110 degrees of active flexion and was ½ inch greater in circumference than the left. She was engaged actively in her secretarial work.

DISCUSSION

It would appear that extended lumbar sympathectomy was effective in the relief of articular pain in 6 of the 7 patients reported. The relief of arthralgia endured for follow-up periods ranging from four to twenty-four months. The single therapeutic failure (Patient J. R., Case 6) arose from a technical difficulty in the

operative procedure which precluded the safe removal of the second lumbar ganglion. Evidently resection of the sympathetic chain should be proximal to the second ganglion for adequate denervation of the knee joint. Extended lumbar sympathectomy can be safely carried out by way of an oblique incision in the flank extending caudad from the eleventh rib. It has not been necessary to employ the high lumbar sympathectomy approach of Lilly (17), involving resection of the eleventh or twelfth ribs.

Extended sympathetic denervation, even in the aged patients in this small group, was free of morbidity other than the wound infection in Patient D. G. (Case 2). Intraoperative and postoperative shock did not pose a problem; and transfusion was not necessary. The operation can be employed safely even in the cases of prolonged immobilization and invalidism so commonly seen among patients with advanced arthritis in the lower extremities.

Charcot-like arthropathy was not observed in any of these patients at the time of follow-up examination. Moreover, neuropathic joints have not been reported in the literature following sympathetic denervation, surgical or chemical, for any indication (18).

The effect of articular denervation, extended sympathectomy in particular, on the ultimate course of osteoarthritis or rheumatoid arthritis is conjectural. Postoperative x-ray studies made up to two years after operation have not revealed any significant change in the roentgen appearance of these joints. It is unlikely that this procedure would alter the basic pathologic condition involved in the arthritic process.

A theoretical objection to denervation as a method for relief of pain in arthritic joints is that obtundation of pain sensation permits the patient a degree of physical activity which would increase stress on a previously damaged joint surface. Actually, after extended sympathectomy these patients have observed that prolonged weight-bearing and articular motion produces a vague sensation of localized fatigue in the denervated joint, and this provides a warning against continued activity.

The physiologic rationale for extended sympathetic denervation of painful joints is based on the surgical ablation of afferent pain fibers which run from the joints into the paravertebral lumbar sympathetic trunks. It does not seem likely that the cessation of articular pain following the operation is a function of an adrenocortical response to nonspecific surgical stress. The only joints which exhibit relief of articular pain are those in the extremity which has been denervated. Pain in the joints of other extremities in the same patient remains unaffected.

That there is a major sympathetic representation in the innervation of synovial membranes and articular ligaments is not accepted by all observers (1). There is, nevertheless, increasing evidence that this is true. Gardner (18) maintains that articular pain arises from stimulation of the perivascular autonomic receptors in the capsules of the joints and the synovial surfaces. Kellgren and Samuel (19) have found that the sensation of pain in the human knee joint arises from the fibrous articular ligaments and to a lesser degree from the synovial membranes. The same investigators have demonstrated histologically that the majority of

nerve endings in the articular ligaments and synovia are of autonomic origin. They suggest that somatic peripheral nerves contribute to the innervation of the joints, but to a minor degree. This insignificant contribution of somatic fibers to the afferent pathways from arthritic joints may explain the transient and incomplete relief of arthralgia following peripheral neurectomy.

Additional evidence for the sympathetic innervation of articular surfaces is available in recent pharmacologic studies. Howell (20) used tetraethyl ammonium bromide, a ganglion-blocking drug, in a series of 26 patients with rheumatoid arthritis; only transient diminution of pain was obtained. Platt and Steinberg (21), after noting the clinical similarities between chronic rheumatoid arthritis and the reflex sympathetic dystrophies, treated 12 arthritic patients with hexamethonium chloride and observed only temporary relief of pain.

The effect of extended sympathectomy on the periarticular tissues, principally the tendinous expansions of skeletal muscles, is not clear. These structures are involved in rheumatoid arthritis and, thereby, contribute to immobility of the joint by means of reflex spasm (18). Bremer (22) states that Hunter and Boeke noted a sympathetic nerve supply in striated muscle. This autonomic innervation has been interpreted as the source of muscle tone in normal skeletal muscle and tendon. If this be true, it follows that extended sympathetic denervation allows for relief of periarticular muscle spasm and pain.

The disability of the patient with advanced arthritis in the weight-bearing joints is the result of articular pain and limitation of motion. Much of the immobility in the joints is a function of the pain. Sympathetic denervation lessens the disability of these patients by its primary effect on articular pain and the secondary effect on immobility.

SUMMARY

Extended lumbar sympathectomy, encompassing lumbar sympathetic ganglia with accessory ganglia and decussating fibers, has been employed as a procedure for denervation of joints in 7 patients with advanced painful arthritis in the lower extremities. In this small group, extended sympathectomy has been an effective method of providing relief from intractable articular pain in both osteoarthritis and rheumatoid arthritis. On the basis of results observed during follow-up periods ranging from four to twenty-four months, the relief of pain and immobility has been lasting.

Extended lumbar sympathectomy appears to be an effective modality in the treatment and rehabilitation of patients with painful arthritis of the hip and knee joints.

Addendum

An additional 3 patients have been operated on, employing extended lumbar sympathectomy, since this report was submitted for publication. These patients have noted marked alleviation of pain in the hips and knee joints since operation.

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HOST-TUMOR ANTAGONISM. IX. THE RETICULO-ENDOTHELIAL SYSTEM AND NEOPLASIA*

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I. INTRODUCTION

The relationship between depressed reticulo-endothelial function and neoplasia has been the subject of much research. Although a definitive correlation cannot as yet be made, the concept that the reticulo-endothelial system plays a fundamental role in neoplasia has resulted in important theoretical and even some modest practical results. This system is not an anatomic or histologic entity, but rather a functional unit.

The units in the system are bound together because of their ability to store colloids, and their participation in immunologic, chemical and metabolic processes. Some of the units have exceedingly specialized functions. Although the spleen contains the largest aggregate of reticulo-endothelial elements in the body, it contains many other structures not related to that system, which serve different purposes. Therefore, the effects of extirpation of the spleen, for example, cannot be considered as due solely to the effects on the reticulo-endothelial system. A masterful discussion of the reticulo-endothelial system in relation to neoplasia can be found in the book by Stern and Willheim (1).

In the present essay, the morphologic and functional activities of the reticulo-endothelial system will be considered. Many investigators have used the hypothetical relationship between the reticulo-endothelial system and tumors as the basis for a therapeutic regimen, *i.e.*, attempts have been made to enhance the activity of the reticulo-endothelial system for the purpose of combating malignant tumors. Methods of enhancement by means of antireticular cytotoxic serum, choline, and bacterial toxins will be discussed.

II. MORPHOLOGIC AND FUNCTIONAL UNITS OF THE RETICULO-ENDOTHELIAL SYSTEM (RES)

The reticulo-endothelial system consists of two groups of cells with similar functions. According to Aschoff (2), this system is composed of (a) the reticulum cells of the splenic pulp, as well as the follicles and pulp cords of the lymph nodes and other parts of the lymphatic apparatus, and (b) the endothelial cells of the lymph-node sinuses, the blood sinuses of the spleen, the Kupffer cells of the liver, and the capillaries of the bone marrow, adrenal cortex and hypophysis (Fig. 1).

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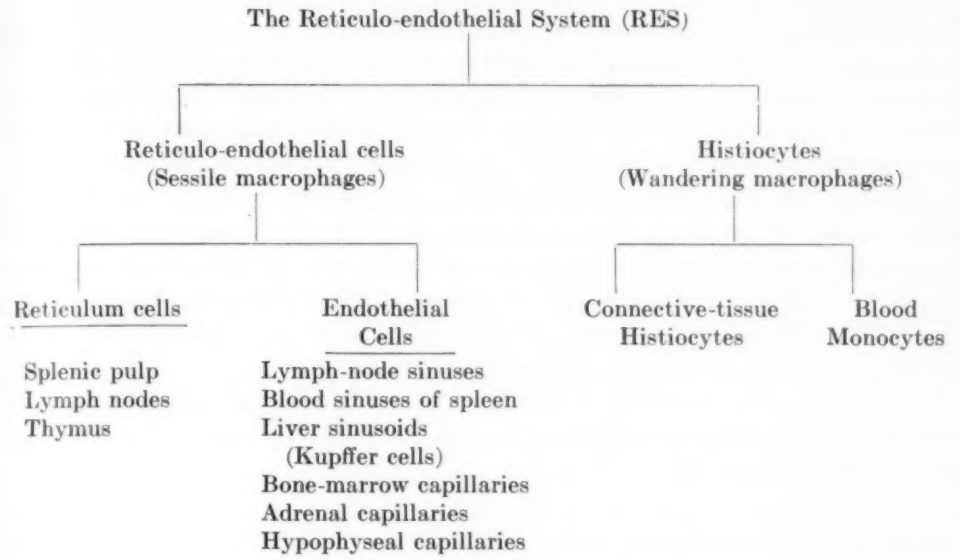

FIG. 1. The Reticulo-endothelial System (after Raffel (3))

Quantitatively, most of the cells are found in the hematopoietic tissues. They are mononuclear cells of mesodermal origin, and are grouped together because of similarity in phagocytic activity, reaction to vital dyes, and certain normal and pathologic functional manifestations. The place of the reticulo-endothelial system in hematopoesis is not entirely settled. Phagocytosis of blood cells is observed in certain conditions, and is considered a function of RES. It is certain that the Kupffer cells are concerned with the formation of bilirubin. Cells of the RES phagocytize platelets and play a part in thrombocytopenic purpura (4).

Many studies point to the part played by the RES in inflammation and in the immune process. For instance, the spleen (as an organ of the RES) has been either extirpated or blockaded with colloidal substances, and the effect on antibody formation has been noted. An exact appraisal is difficult, because the spleen contains lymphocytes in large aggregations, and often plasma cells, in addition to cell types comprising the RES (3).

At the present time, it is believed that the plasma cells are the largest producers of antibodies. Fagraeus (5) demonstrated the formation of antibody in experiments involving explantation of the spleens of rabbits which had previously received injections of antigen. He showed that the red pulp of the spleen (containing many plasma cells) produced large quantities of antibody, whereas the lymph follicles, which were explanted separately, produced very little antibody. Fagraeus believed that the plasma cells develop from reticulo-endothelium, and some cytologists believe there is definite evidence of a relationship between lymphocytes and plasma cells. Therefore, regardless of the type of cell which may prove to be the actual precursor of antibody, it is practically certain that the RES is involved.

Pertinent to this discussion is the part played by the RES in limiting the spread

of neoplasms in animals. It has often been stated that malignancies rarely metastasize to the spleen (6). Proliferation of histiocytes and Kupffer cells in the liver and hyperplasia of the reticular apparatus of the spleen have been found in tumor-bearing animals. This is also true in animals treated with chemical carcinogens, especially if they have proved to be refractory; however, when a malignancy has been induced by chemical carcinogens, follicular aplasia of the spleen is sometimes noted. Gross enlargement of the spleen has been observed in animals bearing neoplasms. Splenic hypertrophy can be induced in animals by injections of blood from animals or human subjects having tumors. Splenic hypertrophy in these instances, can be interpreted as a physiologic defense mechanism, albeit inadequate against the tumor (1, 7).

Conversely, when the RES is blocked by injections of colloids such as trypan blue, there is stimulation of tumor growth. This is also true if the animal has been splenectomized (8).

III. ENHANCEMENT OF FUNCTION OF RES BY ANTIRETICULAR CYTOTOXIC SERUM (ACS)

Bogomolets (9) and his co-workers felt that the functional state of the RES is a potent force in resistance to infection and degenerative disease, and that it inhibits the growth of metastatic cancer. Based on this premise, Bogomolets prepared an antiserum that was supposed to activate the RES, if given to the animal in small doses. He stated that this antiserum, (antireticular cytotoxic serum or ACS) possessed carcinolytic properties. He further believed that the functional capacity of the RES in humans could be improved by stimulation with ACS which was produced in animals by injections of cells from the spleen and bone marrow from human cadavers.

Fedyushin (10) demonstrated that small doses of ACS decreased significantly the number of successful cancer transplants, caused the disappearance of already developed cancers, and reduced the number of metastases in mice. Kavetsky and Dyadyusha (11) injected small doses of ACS into rabbits bearing transplanted Brown-Pearce tumors and noted a reduction of metastases from 58 per cent in untreated rabbits to 20 per cent in ACS-treated animals. Dyadyusha (12) further noted a reduction of "takes" of a transplanted rat carcinoma from 83 per cent to 21.4 per cent. Further, Pomerat and Anigstein (13) found that the undiluted serum inhibited growth of "Walker rat sarcoma № 319" culture *in vitro*.

Heiman and Meisel (14) in three detailed studies came to the following conclusions:

1. When the injection of ACS was made, either before or after the implantation of tumor fragments of benign adenofibroma (rat sarcoma 39 or rat mammary carcinoma R2426), there was no decrease in the rate of tumor growth or the percentage of "takes" when compared to results in normal untreated controls.

2. ACS made by injecting rabbits with spleen antigen from normal mice or from mice with sarcoma 180 failed to control the growth of spontaneous mammary adenocarcinoma or transplanted mouse sarcoma.

3. The incidence of spontaneous mammary adenocarcinoma in R3 female mice was significantly reduced from 59 per cent to 11.1 per cent after injection of ACS in the precursor stage. The ACS was prepared from spleens of normal mice from strains that do not develop spontaneous mammary cancer or from spleens of female mice with spontaneous mammary cancer.

The last conclusion requires explanation. Heiman and Meisel doubt that the hormonal or genetic factor in cancer development is affected by ACS, but the milk factor may be neutralized by the antiserum before the factor localizes in the mammary glands. Bittner (15) injected fragments of splenic tissue subcutaneously in mice and induced mammary cancer. Andervont and his co-workers (16) believe that splenic tissue may contain a virus-like factor resembling the milk factor. Mammary tumors were induced in 52 per cent of susceptible mice with injections of spleen extract.

Heiman and Meisel (14) believe that the reduced incidence of spontaneous mammary cancer in female R3 mice may be due to the destruction of the virus-like milk factor by the rabbit ACS. This milk factor, which is distributed in all the viscera may not be fixed in the precancerous stage. It may therefore be possible for the rabbit antiserum to neutralize the milk factor before it has initiated abnormal cell division leading to carcinogenesis.

The use of antireticular cytotoxic serum was suggested by Bogomolets (9) as a postoperative measure in human cancer, for the relief of pain in inoperable cancer, for treatment of lymph node metastases, and for prevention of recurrences. Although the Russian reports appeared promising, the results in this country have been meager.

Among other reports, is the study of Skapier (17) which showed that although there was no definitive effect in patients with Hodgkin's disease, there was a transient gain in weight and a decrease in the erythrocytic sedimentation rate.

Movitz, Saphir and Strauss (18) attempted to determine the antineoplastic properties of ACS *in vivo* in rabbits implanted with Brown-Pearce carcinoma. Various dosages were given at varying time intervals. In 3 series, in which the dose of ACS was measured in hundredth's of a cubic centimeter and given at 48-hour intervals, there was enhancement of the malignancy. In other series, when slightly more than one thousandth of a cubic centimeter was given at seven-day to nine-day intervals, there was a favorable effect in ACS-treated rabbits compared with control rabbits, regarding survival time and spread of malignancy (so-called malignancy level in the author's paper). Thus, both dosage and time factors were critical in determining whether cytotoxic (enhancement of malignancy) or cytostimulatory (regression of malignancy) effects were obtained.

Dosage and time factors may have played a crucial role in the failure of ACS as an adjuvant in the therapy of human malignancy. If Heiman and Meisel's work on the effect of ACS in the prevention of spontaneous mammary carcinoma in mice can be confirmed, a possible prophylactic use could be envisaged. However, a "milk factor" in the development of human mammary carcinoma has never been proved.

IV. ENHANCEMENT OF FUNCTION OF THE RES, AND ADJUVANT TREATMENT OF MALIGNANCY, WITH CHOLINE

Various methods, including whole body irradiation (19) and cortisone (20), have been used to depress the RES. Some substances, such as trypan blue, apparently damage the RES, then produce a hyperfunctional state (21). It is claimed that various other substances, such as ACS and histamine, stimulate the RES. However, the practical value of ACS in stimulating the RES remains in doubt. It has now been reported that choline causes hyperfunction of the RES (22).

Chevremont (23, 24) found that choline stimulated histiocyte formation in tissue culture. Heller (22) used the rate of phagocytosis of radioactive chromium phosphate as a test of function, and demonstrated that choline caused a 100 per cent increase in function of the RES compared to the condition in controls treated with saline. Heller (20) further showed that the depressing effect on the RES of 0.25 mg. of cortisone could be completely abolished by administration of an adequate amount of choline.

Under the circumstances, it was of great interest that several German investigators claimed that choline was of benefit in carcinoma, either alone, or as an adjuvant to radiation therapy. However, these authors had a distinctly different rationale for the use of choline in the treatment of carcinoma.

Fecht (25) was of the opinion that in vagotonic persons carcinoma rarely develops, and if it does, it is usually not highly malignant. Conversely, sympatheticotonic persons are particularly prone to cancer. He stated that it was possible to inhibit the local growth of carcinoma by cutting the afferent sympathetic nerve fibres. He attributed the favorable effect of roentgen-rays partly to stimulation of the vagus nerve, and thought that increased vagal tone enhanced the effect of insulin, thereby lowering the level of blood sugar and thus the nutrition of the tumor. According to Fecht, choline produces inflammatory reactions in the carcinomatous lesion, and this inflammation stimulates rather than prevents healing, since it increases local resistance. He further believed that a cholesterin-rich diet may be one cause for the increasing incidence of carcinoma, as cholesterol apparently suppresses vagal activity and supports sympathetic activity. Choline counteracts this effect of the cholesterol in his view.

Fecht found that in animal experiments, neostigmine (Prostigmin)—which is an even more intensive vagal stimulating substance—had an effect similar to that of choline, namely, inhibition or complete disappearance of the carcinoma. Following pretreatment with choline or Prostigmin, the carcinoma implants failed to grow in 70 per cent of the animals. Fecht stated that in man the results of treatment of carcinoma carried out on the basis of these findings were in agreement with the results in animals.

Becker (26) found that choline therapy combined with irradiation produced considerable improvement in hopelessly ill patients. Becker gave his patients 2 to 10 grams of choline daily, at the rate of 0.5 or 1.0 gram every one or two hours during the day. The tumors appeared to be inhibited in growth, but did not disappear. Improvement was noted in 25 per cent of 80 severely ill patients.

Velten (27) stated that there was a definite change in the character of the growth of tumors in patients who had been treated with choline. When the drug first took effect there was a marked inflammatory cellular reaction, which was followed in the course of choline therapy by the gradual devitalization of the tumor cells. Finally, after prolonged treatment, connective tissue had replaced the tumor tissue. The condition necessary for effective treatment appeared to be long-continued high dosage.

The findings in human tumors have been confined to several studies of solid mouse tumors. Lettre (28) reported that the effect of choline on mouse-ascites tumor consisted of an increase in giant cells in the metaphase, with inhibition of division of cytoplasm in the anaphase.

Gansslen (29) believes that the therapeutic effect of choline is one of physiologic inhibition of growth and that there is no specific effect on tumor cells. In mature cells this results in a life-prolonging, protective effect. In cancer cells it has been found that choline inhibits the dissolution of the cellular nuclear membrane and leads to the formation of giant cells.

These unstable giant cells are rapidly destroyed and prevent further cell proliferation. Gansslen found that sulfonamides acted also in this manner on cancer cells, so he combined sulfonamides and choline as a suitable form of basic treatment in tumor control. During the course of years, this author claims to have treated more than 100 inoperable tumors with choline. He stated that although the results were variable, they were beneficial in many cases.

Kraus (30) felt that choline might inhibit the growth of immature cancer cells. He administered choline citrate to carcinoma patients orally, in a total daily dosage of about 1.75 Gm. of choline. In some instances, a decrease in the size of the tumors was noted. Kraus recommended that choline medication be continued for a long time.

Becker (31), in another study, used choline therapy in patients with tumors which were not suitable for treatment with surgery or radiation. He used choline chlorate in a daily dosage of 5 to 15 Gm., depending on the condition of the patient and the reaction of the tumor. The choline was administered by intravenous or intrasternal drip infusion; when this was impossible, it was given by intragastric or rectal drip. A 5 to 25 per cent solution of choline chlorate was used. The patients' general condition improved after the first few infusions, associated with increased appetite and a slow gain in weight.

The most impressive finding was the definite affinity of choline for the tumor. There was a definite local reaction consisting of pain, redness and swelling in the region of the tumor and the metastatic nodules. For the first few days the tumor became smaller and harder. Lymph-node metastases were influenced more rapidly than the primary tumor. In some patients the ascites disappeared and did not recur. Necrosis was rare in the tumor region.

The first perceptible histologic changes occurred after about 60 to 80 grams of choline had been given. The tumor became more sharply demarcated from the surrounding tissue. There was also proliferation of connective tissue. Collections of inflammatory cells, chiefly leukocytes, were seen in the immediate neighbor-

hood of the tumor cell complexes. Becker felt that the choline combined with the malignant cells and produced macroscopic and microscopic changes, and also acted indirectly on the vegetative nervous system.

Whatever the explanation offered by these German authors for the efficacy of choline as adjuvant therapy in human carcinoma, their reported results require attention. A controlled clinical trial is definitely indicated.

V. TREATMENT OF MALIGNANT TUMORS BY BACTERIAL TOXINS

The treatment of malignant tumors by bacterial toxins is based on the fact that neoplasms have been known to regress during acute bacterial infections, principally erysipelas, but also after acute tuberculosis and smallpox. The inhibitory action was often powerful enough to cause complete regression, and in some instances there were no recurrences. Many cases of "spontaneous regression" of cancer were associated with the development of spontaneous or induced erysipelas in the tumor or in the wound, or the use of Coley's toxins. To call these regressions "spontaneous" is really begging the question. A specific modality had been employed, and the regression may have been no more spontaneous than if it had occurred after radiation or surgery.

Busch (32) is usually credited with being the first physician to invoke the help of erysipelas infection to cause the regression of cancer. However, Collis (33) had discussed this idea at least ten years before. He emphatically stated that when a patient recovers from a severe attack of erysipelas after the removal of a cancerous part, there is less likelihood that the cancer will recur.

In 1868 Busch (34) reported on the dramatic regression of inoperable sarcoma in 2 patients who had contracted erysipelas. He attempted to induce erysipelas in certain patients having malignant disease, but was largely unsuccessful. The etiologic organism of erysipelas was discovered in 1882 by Fehleisen (35), who promptly used it for the induction of erysipelas in cancer patients.

After noting that Busch had tried to treat inoperable malignant neoplasms of the lymph glands by means of erysipelas, Fehleisen was successful in infecting a patient by placing her in a bed in which patients with open wounds usually contracted erysipelas. The desired effect was obtained. The tumor, which was an extensive lymphosarcoma of the neck, disappeared except for a small portion; this portion, however, again became enlarged. This result was only partially satisfactory, but it encouraged further trials. Fehleisen reported the results in a personal series of 7 cases in which he attempted to induce erysipelas. There were some partial regressions, and in 1 case of thrice-recurrent mammary cancer there was complete regression.

W. B. Coley became interested in the phenomenon when an inoperable lymphosarcoma of the neck, which had recurred postoperatively three times, regressed following an attack of erysipelas. Beginning in April 1891, Coley (36) attempted to produce erysipelas as a therapeutic agent in 10 patients with inoperable malignant lesions. It was difficult to induce an attack, and often dangerous if it finally occurred. He tried cultures of Strept. erysipelatis sterilized by

heat or filtration, but these were found to be weak and ineffective. A short while later, he learned that the toxins of B. prodigiosus could increase the virulence of other organisms, if the association occurred during the proliferative state (37).

Various mixed toxins were developed under Coley's direction, some of which were weak, and others effective (38). There are patients alive today who recovered from inoperable sarcomas after having been treated with a toxin mixture by Coley or under Coley's direction. Some of the cases of the so-called spontaneous regression of cancer have been in patients who were treated with Coley's toxins.

Coley usually employed intratumoral injections of toxins in his early work, and these apparently produced the best results. Intramuscular injections were relatively ineffective. Intravenous injections were more effective than intramuscular, and were better borne by the patient (38).

Fowler (39), an enthusiastic observer and one of the most brilliant surgeons of his time, stressed the importance of producing definite reaction, *i.e.*, at least two or three well marked reactions in a week, and continuing therapy for three or four months. He found it interesting that fever due to erysipelas or to the mixed toxins should prove destructive to neoplastic cells, whereas fever due to other diseases did not have this effect.

Recently Nauts, Fowler and Bogatko (40) critically analyzed 30 cases out of over 270 inoperable cases of malignant tumor in which complete regression was obtained. No other therapy has claimed so many regressions in inoperable cases. The authors describe the first patient treated with Coley's toxins—a young man with inoperable spindle-cell sarcoma of the abdominal wall and pelvis, involving the bladder. The extensive growth disappeared and the patient remained free from recurrence until he suddenly died from heart disease, twenty-six years later. Treatment was continued for four months and the injections were intratumoral.

About 15 different formulae of Coley's toxins have been used during the past sixty years. Some of these were admittedly weak, but even these were occasionally successful in certain patients, although not potent enough to cause regression in the resistant type of neoplasm. Only 4 of these preparations were considered potent by the authors.

Another patient, a woman aged 29, had an extensive inoperable fibrosarcoma of the abdominal wall which was treated by Coley's toxins. She received intratumoral injections for four months. There was no recurrence after the initial regression, and she died twenty-five years later of heart failure. An autopsy showed no evidence of tumor.

Another patient, a girl aged 16, had an inoperable spindle-cell sarcoma of the scapular region, with extensive involvement of the chest wall. This was an extremely rapidly growing tumor. She was treated for nine and a half months by intratumoral injections. The growth regressed entirely by absorption, without breaking down or sloughing. She remained in good health and had no recurrence when last traced nineteen years later.

Another typical patient, a woman aged 27, had a round-cell sarcoma involving the kidney and retroperitoneal lymph glands. The tumor could not be removed and the patient was expected to die shortly. Injections of Coley's toxin were

given intramuscularly in the buttocks. She began to improve quite unexpectedly, and had remained well (when last traced in 1952) over forty years after onset.

Even if the Coley toxins were to have caused a regression of only 1 tumor, its mode of action in this 1 case would warrant an attempt at explanation. For the purposes of this essay, it was assumed that stimulation of the reticulo-endothelial system was a possible mode of action of these toxins, though perhaps not the most important action.

Beebe and Tracy (41) injected bacterial filtrates, including filtrates of Strept. pyogenes and B.prodigiosus, into dogs bearing transplanted lymphosarcomas. In many of the dogs, softening of the tumors occurred and sometimes there was complete regression. Shwartzman (42) noted that when bacterial filtrates (especially of Gram-negative organisms) were injected into the skin of normal rabbits, and this was followed in from four to forty-eight hours by an intravenous injection of the same or different filtrates, an intense reaction occurred in the skin at the site of the original cutaneous injection. The local site at first became hemorrhagic and later usually became necrotic. The cause remained obscure. It apparently was not due to local blockade of the reticulo-endothelial cells, or to inflammation or increased capillary permeability.

The work of Gratia and Linz (43) applied the Shwartzman reaction directly to the chemotherapy of tumors. These Belgian investigators injected filtrates of B. coli directly into transplanted liposarcoma in guinea pigs. Twenty-four hours later portions of the same filtrates were injected intravenously, and they observed extensive hemorrhage and necrosis in the tumor masses, but not in other parts of the animal. In other experiments, the same effect on the tumor was observed after injecting the filtrate intravenously, without the preceding injection of the tumor. Gratia and Linz considered that this reaction was possible because of a prior sensitization of the tumor. They postulated that the liposarcoma had been sensitized spontaneously by pre-existing micro-organisms; subsequently finding none, they inferred that a virus had sensitized the tumor, and that cancer was caused by a virus. The inferences may not have been correct, but the data seemed valid. Shwartzman (44) confirmed this phenomenon using a different filtrate and a different animal.

During the next few years, Shwartzman in his experiments tried to protect the host from the toxic effects of the bacterial products. When a sufficient dosage was used, the mortality was extremely high. The observations were further confirmed by Shear (45). One wonders whether the various bacterial filtrates contained an antigen that was identical with an antigenic constituent of neoplastic cells.

Andervont (46) studied the effects on the tumor of intravenous injection of a bacterial filtrate. Within twenty-four hours there was hemorrhage in the tumor, but most of the tumor cells were viable. In the course of a week to ten days, the tumor had often become necrotic, and had sloughed. At this time, microscopic section showed fragmented, poorly stained structures that had been tumor cells.

Shear (45) and his co-workers showed that a filtrate of B. prodigiosus (*Serratia marcescens*) induced hemorrhage and necrosis in transplanted mouse carcinoma. Over the years the active fraction of the filtrate has been isolated, and found to be a polysaccharide. It induced hemorrhage and necrosis in tumor tissue in

dosages as small as a fraction of a milligram. This polysaccharide was subsequently shown to produce necrosis and hemorrhage in transplanted and primary sarcoma and carcinoma. The toxicity, however, was very great, depending on the size of the tumors, as well as on the toxicity of the polysaccharide itself.

The findings of Shear with the polysaccharide prepared from B. prodigiosus seemed to offer an explanation for Coley's empirical observations on the effects of the Coley mixed toxins.

Shear (47) advocated more extensive work on bacterial filtrates. Metabolites from other organisms, and the mechanism of action of such materials, should be investigated.

The use of Shear's polysaccharide in humans has been followed by severe reactions and by only slight regression of tumors (48). No tumor in the series treated at Lankenau Hospital was completely destroyed. However, there were some interesting responses. In 1 case of lymphosarcoma with marked edema of the lower extremities and large nodes in the groin and retroperitoneal area, following treatment the extremities returned to normal size and the nodes seemed smaller. In 1 case of malignant melanoma, a greatly enlarged liver shrank so that its edge could be felt just below the costal arch.

It is possible that the mechanism of action of Shear's polysaccharide and the mixed toxins may be entirely different from that already discussed. It has been shown by Landy (49) that the injection of bacterial lipopolysaccharides derived from a variety of Gram-negative bacterial species evokes in mice a rapid rise in resistance to infection with Gram-negative pathogenic bacteria. This is accompanied by an elevation in the titer of properdin to levels two or three times normal.

In 1954, Pillemer *et al.* (50) isolated a new euglobulin in serum, that they called properdin. In the presence of complement and Mg++, this protein destroys bacteria, neutralizes viruses, exerts a lytic effect on erythrocytes, and is readily destroyed by total body radiation. Herbut and Kraemer (51) theorized that since total body irradiation may destroy an animal's ability to resist heterologous tumor transplantation, this resistance may work through the properdin system. Herbut and Kraemer neutralized the animal's store of properdin by giving it zymosan, an extract of yeast-cell walls which combines quantitatively with properdin. They used normally resistant Wistar rats and attempted to implant human colon carcinoma HR 132. Of 160 animals in each category, the number of tumor "takes" was as follows: 19 in untreated animals, 136 in irradiated animals, 58 in animals given a single injection of zymosan, and 90 in animals given multiple injections of zymosan.

These findings indicated that the properdin system is involved in resistance to heterologous transplantation of tumors, but whether it also is involved in resistance to spontaneous tumors is as yet unknown.

VI. MISCELLANEOUS OBSERVATIONS ON THE PROBABILITY OF REDUCED FUNCTION OF THE RES IN MALIGNANCY

Ungar (52) discussed the evidence for the hypothesis that patients who tend to have inflammatory episodes and infectious diseases have a low incidence of

cancer. In 1910 Schmidt (53) pointed out that in the records of cancer patients a history of infectious disease is found less often than in those of other patients; among 291 carcinoma patients he found 99 who had never contracted an infectious disease. Engel (54) noted that among 300 patients suffering from disease other than cancer there were 16 who had never contracted an infectious disease, whereas among 300 cancer patients there were 113 who had never had an infectious disease.

Schmidt noted that when cancer patients are vaccinated against smallpox, there is usually a weak reaction. Moreover, when a cancer patient is exposed to poison ivy there is only mild dermatitis, in marked contrast to the severe dermatitis that results when normal persons are exposed.

From 68,385 detailed case histories from the University of Basle, of which 4,192 related to cancer patients, it was further shown that in the cancer group there had been a minimal incidence of infectious disease, and that when infectious diseases had occurred, they had been extremely mild. To Ungar, the results of these studies confirmed Billroth's dictum, "It is as though a surplus of good health appertained to the acquisition of a carcinoma."

Jacobsen (55) cited data which purported to prove the low incidence of malignant disease in patients who had been victims of a common infectious process—for example, active tuberculosis or osteomyelitis, typhoid, paratyphoid, scarlet fever or diphtheria. He believed that, 1) an individual is better able to cope with malignant disease when the reticulo-endothelial system is stimulated or chronically irritated by a sufficient number or by sufficient severity of infectious diseases, 2) the present increase in morbidity from malignant disease is due to a decreased power of the reticulo-endothelial system to cope with cancer noxae, whatever they may be, and 3) cancer may be regarded as a disease of the reticulo-endothelial system; thus, activating the RES would be one way of cancer prevention.

Other authorities before and since have held similar views. Shear (47) of the National Cancer Institute stated, "Are pathogenic and non-pathogenic organisms one of Nature's controls of microscopic foci of malignant disease, and in making progress in the control of infectious diseases, are we removing one of Nature's control of cancer?"

Kolischer (56) noted that in certain instances the beneficial effect of a combination of radiation and electrocoagulation in the treatment of cancer was much greater than that of radiation alone. In many cases clinical cures were obtained in cases of cancer which were definitely inoperable by ordinary surgical procedures. In some cases of vesical tumor, incomplete destruction of the tumor by coagulation furnished complete and permanent cure.

Kolischer credited the reticulo-endothelial system, and more specifically its active elements, the macrophages, for this phenomenon. The macrophages are attracted to any part of the body in which there is an increase of metabolism. An abundant migration of macrophages occurs around the zone of electrocoagulation.

Kolischer quoted Cramer and Crabtree with regard to the therapeutic action

of radium on spontaneous mammary carcinoma in the mouse. In radiosensitive tumors there is an invasion of the stroma by macrophages, whereas in radioresistant tumors there is no such migration. These observations indicate that radiosensitivity is not an inherent quality of the cancer cell, but depends on the surrounding stroma, which in turn is influenced by the macrophages.

It would be of great interest if the status of the reticulo-endothelial system could be measured. This can be attempted by means of a test (57) using Congo Red, a colloidal dye which is stored by the RES cells. The Congo Red is injected intravenously; a blood sample is withdrawn soon after, and another sample is withdrawn at a specific interval; the difference equals the amount of dye intercepted by the RES cells. The ratio between the concentrations of dye in the two samples of blood is called the Congo Red index. It is high in patients with cancer. Normal values, after the method of Stern (57), are between 45 and 70. Stern found that in cancer patients with a very high index (90–100), the prognosis was poor; 70 per cent of them died in a short time. In patients who were improved by radiation therapy, the index fell. It is sometimes stated that radiation therapy is accompanied by activation of the RES, but the dosage is critical in this regard.

Stern (57) stated that the function of the RES was damaged in 86 per cent of cancer patients; however, the 14 per cent who had had normal values could not be explained. For some reason, sarcoma patients did not invariably exhibit decreased function of the RES—only 2 of 5 cases had the expected high Congo Red index. It has been noted by Cramer (58) that RES function is less frequently decreased in sarcoma of mesodermal origin, than in epithelial hyperplasia.

A drawback in the measurement of RES function by the Congo Red index lies in the fact that colloid-storing is only one property of the RES, and certainly not the most important one.

VII. PRACTICAL THERAPY OF MALIGNANCY BASED ON PARTICIPATION OF THE RES

It was established by Saphir, Appel and Strauss (59) that Brown-Pearce carcinoma implanted into a Belgian hare and allowed to metastasize into the abdomen would often recede completely when additional carcinomatous tissue was transplanted intracutaneously in the same hare. Normally, the original transplant would metastasize rapidly and cause death in from three to six weeks. The animal in which the cutaneous transplant had been made was subsequently immune to challenge cancer grafts with Brown-Pearce carcinoma. To the authors it seemed likely that the RES had stimulated formation of antibodies, which accounted for the destruction of the original cancer and the peritoneal metastases.

The role of the RES as one of the body's guardians against cancer seemed confirmed, upon observing the results of experiments in which "immune" hares were given trypan blue intravenously over long periods of time, followed by injection of suspended tumor cells. In 7 of 9 animals treated in this manner the carcinoma spread with great rapidity, apparently because of blockage of the RES by the injection of trypan blue (60).

On the basis of the work of Lumsden (61), of Aptekman, Lewis and King (62),

and of Strauss, Saphir and Appel (63) it can be stated that when a successfully (growing) transplanted tumor undergoes necrosis and resorption, certain substances are absorbed by the animals which render them immune to further challenge implants of tumor.

Strauss and his colleagues (63) reasoned that each individual has his own varying resistance to his own cancer, and that this plays a vital role in the length of survival. They felt that normal resistance is augmented when the tumor undergoes necrosis and subsequent absorption.

Since 1913, Strauss and his associates (63, 64) have used electrocoagulation in the treatment of carcinoma of the colon and rectum in approximately 250 patients. Their results have been excellent; 75 per cent of the patients survived for more than five years, 15 per cent for more than ten years, and 15 per cent have lived out a normal life span. These authors believed that electrocoagulation not only produced mechanical destruction of the cancer, but also elicited the formation of antibodies, which then probably prevented the progress of the disease.

Straus *et al.* (63) felt that the immunity acquired in man following electrocoagulation of the tumor may not be as absolute as the immunity described for animals. It appears to be only relative and may have to be augmented, preferably by Coley's toxins. The need for augmentation may be due to incomplete coagulation, to incomplete destruction of the blood supply to the tumor, or to an inadequate amount of antibodies stimulated by the tumor.

SUMMARY

Since the reticulo-endothelial system (RES) is apparently involved in the problem of immunity to cancer, and since there is depression of RES activity in cancer patients, it seemed wise to study ways to stimulate or augment the functions of this system.

There have been many attempts to stimulate RES activity, some of which are described. These include the use of such agents as reticulo-endothelial cytotoxic serum, choline, or bacterial toxins. None of these methods has given entirely satisfactory or practical results. However, some procedures based on these theoretical concepts seem to have resulted in a larger salvage of cancer patients than have the present traditional methods. For this reason, it seems worth while to explore these concepts further.

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CLINICAL USES OF YOGURT

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Yogurt and related fermentation products of milk have long been important articles of diet. Early in the twentieth century, Metchnikoff (1) and his associates recommended recolonization of the colon with lactobacilli from yogurt. Kleeberg (2) and Rosell (3) claimed yogurt and kefir to be complete foods containing all the necessary elements or vitamins in easily assimilable form.

Rettger and Chaplin (4) observed that *Lactobacillus bulgaricus* disappeared from the stools as soon as its exogenous source, yogurt in the diet, was removed. However, *Lactobacillus acidophilus*, a normal inhabitant of the bowel, could be maintained easily when lactose or dextrin was ingested in large quantities.

Yogurt is a fermentation product of milk, which is easily digested because its proteins are partially digested and broken down into intermediate end-products such as albumoses and peptones. Similarly, its milk content is fermented into lactic acid and, to a lesser extent, acetic acid. Its butterfat content, however, undergoes no significant change. The micro-organisms which produce these changes are *Lactobacillus bulgaricus*, *Thermobacterium yoghurti*, and *Streptococcus acidi lactis*. As a result, yogurt consists of fine curds that require no further curdling by rennin in the stomach. Unaltered milk acted upon by rennin in the stomach forms curds harder to digest than those of yogurt.

In 1950, Seneca, Henderson and Collins (5), studying the microbiologic properties of yogurt, found that it possessed bactericidal and protozoicidal activity. It contained a diffusable, filtrable, thermostable antibiotic factor that reached its maximum titer in a week and disappeared in two weeks. This factor was six times more potent in yogurt made from cow's milk than in that made from human milk. The lactic-acid content of yogurt remained constant for three weeks. Yogurt inhibited gram-positive and gram-negative bacteria. All pathogenic and nonpathogenic bacteria, as well as *Endamoeba histolytica*, *Leishmania donovani*, and *Trypanosoma cruzi*, were killed in yogurt, but the spores of *Bacillus anthracis* and *Mycobacterium tuberculosis* survived.

GASTRO-INTESTINAL DISORDERS

Infantile diarrhea

Numerous semiscientific reports claim beneficial effects for yogurt in gastrointestinal diseases or disturbances such as diarrhea, constipation, enteritis, dysentery, colitis, cholecystitis, hepatitis and autointoxication. After using yogurt for twelve years in healthy and diseased infants, Fykow and Mayer (6) reported that the usual intestinal bacteria were replaced by *Lactobacillus bulgaricus* as long as the infants ate yogurt. Infantile diarrhea could be controlled by adding yogurt to the diet. Seneca (7–9) and Ferrer and Boyd (10) obtained good results

with yogurt in the management of constipation. Raffle (11) treated 20 infants having gastro-intestinal infection or enteritis, caused in 19 by pathogenic *Escherichia coli* and in 1 by *Salmonella typhimurium*. Oxytetracycline (Terramycin) and yogurt were given by mouth and fluids were given intravenously. The infants received 15 to 20 mg. of oxytetracycline per kilogram of body weight daily for seven days in divided doses. Yogurt was started on the fourth or fifth day and continued for at least three days after lactobacilli were grown from the stools. This combined treatment eliminated *Escherichia coli* from the feces. Infants given yogurt improved quickly and steadily gained weight. Nineteen were cured in three weeks and had lactobacilli in their stools. The infant with the *Salmonella typhimurium* infection required treatment a second time to eradicate the infection. Eighteen patients followed for six months had no relapse.

Reactions to antibiotics—micrococcal enterocolitis

With the introduction of antibiotics and particularly with increased use of broad-spectrum antibiotics, a new clinical entity due to disturbance of the biologic or microbiologic equilibrium of the intestinal and respiratory tracts has been frequently observed. This condition may range from mild diarrhea with pruritus ani or pruritus vulvae to severe and often fatal micrococcal enterocolitis or generalized moniliasis. For example, Pelner and Puderbach (12) recently cited 25 references to micrococcal enterocolitis.

A delicate balance exists among the bacteria normally present in the bowel and respiratory tract. During antibiotic therapy, sensitive organisms are killed, while resistant organisms grow unopposed, thus giving rise to superinfection. Antibiotic resistant strains of *Micrococcus pyogenes aureus* are the primary source of trouble. They give rise to pseudomembranous enterocolitis. *Candida albicans*, *Pseudomonas aeruginosa*, *Proteus*, and enterococci also have caused this condition. Recently, *Aerobacter aerogenes* has manifested increased resistance to antibiotics and therefore should be kept under observation.

Treatment for micrococcal enterocolitis requires immediate stopping of the antibiotic. Symptomatic and systemic administration of drugs, fluids and electrolytes should then be started, as well as of antibiotics and antibacterial agents specific against the causative organism or organisms. In the case of micrococcal superinfection, the following drugs are recommended: erythromycin, carbomycin, novobiocin, oleoandomycin, bacitracin, neomycin, and sulfonamides. In *Candida* infections, nystatin is the only choice. In *Proteus* or *Pseudomonas aeruginosa* infections, polymyxin, streptomycin, chloramphenicol, cycloserine, nitrofurantoin and even sulfonamides may be tried. The best plan is to select the most suitable drug after making a sensitivity test using the tube dilution method. In severe cases, ACTH, prednisone or prednisolone have been used. Pruritus can be controlled by applying prednisolone (Meticortelone) ointment.

The patient's diet should be supplemented with vitamins. Yogurt or specifically cultured buttermilk of Bulgarian variety should be fed in order to reinhabit the intestinal tract with lactobacilli which can inhibit or control the bacteria causing the superinfection. Lyophilized, dehydrated and preserved lactobacilli

have been used, and a few commercial preparations are available. However, our experience has shown that viable lactobacilli cannot be preserved for a long time in either lyophilized or dried form. We cultured such preparations for lactobacilli and were disappointed to find that the organisms had lost their potency or viability. The cheapest and best source of *Lactobacillus bulgaricus* is yogurt. In case of objection to the taste of yogurt, the next choice is cultured buttermilk. However, we prefer to use yogurt.

Acute and chronic bacterial and amebic infections

For six or seven years, we have used broad-spectrum antibiotics in the treatment of acute and chronic bacterial and amebic infections. Although minor side-effects such as diarrhea, pruritus, and nausea have been observed, major complications such as severe superinfections have been rare. Perhaps this is because we administer yogurt or cultured buttermilk during the course of treatment with antibiotics and for a few weeks thereafter. When neither is taken with an antibiotic, the appearance of diarrhea or pruritus warns that one or the other should be ingested.

Recently, we have used antibiotics in combination. An ideal combination is tetracycline, novobiocin, and nystatin in equal amounts. This combination not only controls micrococcal and monilial superinfections, but also exerts a synergistic effect upon cultures of bacteria and of *Endamoeba histolytica* (13, 14). Other combinations which exert a synergistic effect and control micrococcal superinfections are tetracycline with novobiocin (13, 14), tetracycline with oleandomycin (Sigmamycin) (15), and tetracycline with novobiocin or vancomycin (16).

It is feasible to reinforce the lactobacillus population of the intestinal tract of adults and infants by the ingestion of yogurt or cultured buttermilk. The addition of *Lactobacillus bulgaricus* to an infant's formula may eliminate or reduce to a minimum pathogenic bacteria and *Escherichia coli*. As most cases of infantile diarrhea in temperate climates are caused by *Escherichia coli* rather than by *Shigella* or *Salmonella*, it should be possible to inhibit the growth of these coliform organisms by maintaining an effective population of lactobacillus in the intestinal tract. The most readily available source of these organisms is yogurt.

Geriatrics

Yogurt plays an important role in geriatrics. Regulation of bowel movements and proper functioning of the intestinal tract are of utmost importance in old age. The bacterial and lactic acid content of yogurt, and its antibacterial principle help to correct constipation or diarrhea or both, as well as intestinal intoxication due to colonic dysfunction. The easy digestibility of yogurt compared with that of milk is an advantage in old age. Osteoporosis, a natural process in old age, may be favorably influenced by the ingestion of yogurt, the calcium and phosphorus of which can be easily absorbed and assimilated.

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MANAGEMENT OF THE "GERIATRIC SYNDROME" WITH NUTRITIONAL-HORMONAL SUPPLEMENTS

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In any practice involving patients over 60 years of age, a great many problems not encountered in younger age groups must be faced by the physician. Relatively recently this form of medical practice has been given the name of geriatrics. Some writers, thinking more broadly and including the socio-economic aspects of aging along with the medical implications, have applied the term gerontology to the entire field of aging and older citizens.

No matter what name is used, however, patients over 60 pose a great challenge to the physician. They are subject to the same acute illnesses that occur in people of any age group. Such conditions must be handled promptly, because even a relatively minor illness in the older patient can lead to chronic disability if active care and rehabilitation are not instituted at once.

In addition to acute illnesses, however, there is a wide variety of chronic ailments. Many such conditions have been present for years and are detected only when the patient is forced to seek medical care for some other more pressing problem.

Many of the complaints of patients over 60 are subjective, and of relatively mild nature. No one symptom seems to predominate and even a careful history may elicit only vague and limited information about what is bothering the patient.

After seeing many of these patients in the past ten years, I have begun to refer to this symptom complex as the Geriatric Syndrome. This syndrome is best described as a group of minor symptoms, each of little concern by itself but, when combined, affecting the patient and hindering active participation in work or play. The subjective symptoms are a feeling of malaise and lassitude, a tendency toward fatigue, dyspepsia, weakness of the legs and dizziness.

The changes accompanying aging

Carlson and Stieglitz have identified 8 progressive changes which accompany aging and are not due to specific diseases (1). It is possible that these systemic changes, in part, account for the symptoms so often observed in the older age group. The 8 physiologic and metabolic processes which have been identified are:

1. Gradual tissue desiccation.
2. Gradual retardation of cell division, capacity for cell growth and tissue repair.
3. Gradual retardation of the rate of tissue oxidation (lowering of the speed of living, or in technical terms, the metabolic rate).
4. Cellular atrophy, degeneration, increased cell pigmentation and fatty infiltration.

5. Gradual decrease in tissue elasticity and degenerative changes in the elastic connective tissues of the body.
6. Decreased speed, strength and endurance of neuromuscular reactions.
7. Progressive degeneration and atrophy of the nervous system, and impairment of vision, hearing, attention, memory and mental endurance.
8. Gradual impairment of the mechanisms which maintain a fairly constant internal environment for the cells and tissues (homeostasis). Sufficient weakening of any one of the numerous links in the complex process of homeostasis produces deterioration.

These changes are a continuous and complex process. To a great extent they can explain the loss of muscular strength, vigor, speed of reaction, and acuity of vision and hearing which distinguishes the aged as a group.

Dietary deficiencies

The problem is even further complicated, however, because seldom do older patients eat a balanced diet, and their vitamin requirements are usually inadequately supplied (2). There are several reasons why a poor diet is so common in this group. Elderly people often have poor or few teeth or improperly fitted dentures. Difficulty in mastication means that the patient is apt to avoid meat and other protein foods, and use a relative excess of the more easily chewed carbohydrate foods.

Fixed incomes, usually very low, may further serve to limit the availability of proteins, fruits and fresh vegetables and, again, lead to increased utilization of carbohydrates (3). It appears definite that elderly persons, once the family has been raised and they are alone, take little interest in foods and are prone to eat whatever is most readily available or simplest to prepare.

A combination of the known physiologic changes occurring in the aging process and inadequate diet due to the factors just mentioned, often gives rise to vitamin deficiencies which may be obvious or masked. Such deficiencies further impair the functioning of the older patient. Deterioration in gastric, pancreatic and hepatic functions due to aging further interferes with the proper absorption of the food that is available and increases the difficulty in management.

Nutritional-hormonal supplements

On this basis it seems that the physician, in addition to correcting acute physical disturbances, should be concerned with combating the complicated processes of aging in his patients over 60 (4). In preventive geriatrics, no single agent or chemical substance is adequate for prophylaxis; a combination of several therapeutic agents appears indicated. As may be seen by a review of the physiologic changes accompanying aging and a brief consideration of the socio-economic factors which complicate it, there is need for the following nutritional supplementation:

1. Nonstimulatory gonadal hormones.
2. Hematinic agents.
3. Digestive enzymes.

4. Vitamin and mineral supplements.
5. Protein.

All of these factors are found in the 5-factor geriatric preparation, Neobon.[1] It was used in this study of 25 selected geriatric patients (8 men and 17 women) who had been under my care for several years. Each patient was selected because of a major medical problem in addition to the symptoms previously described as constituting the Geriatric Syndrome. The following are some typical case histories illustrating the response to this nutritional-hormonal therapy:

Case 1. E. P. This 73-year-old woman had always enjoyed good health. Shortly before admission her blood pressure had fluctuated between 170/90 and 200/100. Several months previously she had had an attack of mild cerebral vascular spasm but recovered without permanent disability as far as paralysis of the extremities was concerned. She was treated conservatively with sedation and aminophylline. Her chief complaint following the vascular accident was that of generalized weakness and a decline in energy and stamina. Results of laboratory studies were within normal limits. Therapy was started with 1 capsule of Neobon, three times a day.

Within two weeks the patient reported that she was feeling better, did not tire so easily, and was able to stand and walk. Four weeks later she was seen again. Although not as active as prior to her slight stroke, she was markedly improved. Her daughter was able to leave her, and the patient was able to care for herself and do her own light housework.

Case 2. C. S. The chief complaint of this 83-year-old woman was frequent urination and the lack of "pep." She had an invalid son to care for. Because of mild cardiac decompensation, she was digitalized and the cystitis was treated with antibiotics. She continued to complain of generalized weakness. Neobon therapy was started in a dosage of 1 capsule three times a day. In four weeks she reported that she no longer tired as readily, and three weeks later she was able to carry on her normal chores. Once again she resumed caring for her invalid son.

Case 3. N. C. This 63-year-old asthenic woman had a variety of complaints, based largely on previous diagnoses of anemia. She also complained of frequent extrasystoles and other psychosomatic symptoms. She said she felt tired, and had excess flatus and cramping in the upper abdomen. These symptoms were not completely relieved by belladonna derivatives, so Neobon was started (1 capsule three times daily). Within three weeks there was marked improvement. Gastro-intestinal symptoms and weakness had disappeared.

Case 4. A. G. This 73-year-old man has severe osteoarthritis and arteriosclerotic heart disease. He complained of severe dizziness and weakness. Within two weeks after Neobon therapy was instituted, he reported that he was feeling better, although dizziness persisted. After six weeks, despite some residual dizziness, he no longer complained of fuzzy vision, and he returned to his own apartment to care for himself. He stated that the pain in his knees and wrist joints was much less, although objectively the arthritic processes appeared unchanged.

Case 5. E. W. This 73-year-old woman complained of weakness, nausea and inability to get out of bed. She had marked hypochromic anemia. Liver, iron, and vitamin B_{12} were administered. Her blood count improved but she still was weak and had no appetite. Neobon was started, and after six weeks her nausea had disappeared and she was getting up in the morning helping her daughter get the children ready for school. She appeared to be active and relatively symptom-free.

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[1] J. B. Roerig & Co., Div. of Chas. Pfizer, Inc. Neobon contains small quantities of methyltestosterone, ethinyl estradiol, glutamic acid, pancreatic and liver-stomach substances, rutin, l-lysine, and various vitamins and minerals.

COMMENT

Of 25 patients manifesting the Geriatric Syndrome and treated with Neobon capsules, 23 showed a marked response to the therapy. Two others improved, and none exhibited any side-reactions that could be attributed to the medication.

It is too much to expect that any nutritional-hormonal supplement given to geriatric patients can effect striking or miraculous cures, but this type of medication, when used as an adjunct to other therapeutic agents, helps to overcome the mild symptoms of weakness and malaise so often unresponsive to other forms of medical therapy.

SUMMARY

A nutritional-hormonal supplement, Neobon, was administered to 8 men and 17 women with general and senile debility, sometimes accompanied by organic disease and nutritional deficiency. Their ages ranged from 60 to 84 years. All manifested the Geriatric Syndrome, namely, a feeling of lassitude and malaise, a tendency toward fatigue, and dyspepsia, weakness of the legs and dizziness.

Neobon had a beneficial and invigorating effect in the majority of patients with the Geriatric Syndrome, and cardiac disorders were more easily controlled when it was used as adjunctive therapy.

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THE POST-BULBAR DUODENAL SPASM SYNDROME.

II. Diagnosis and Therapy in the Older Age Group*

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The post-bulbar duodenal spasm syndrome in patients over 50 years of age is a clinical picture of gastro-intestinal invalidism without specificity. The cardinal symptoms are abdominal pain and diarrhea. In addition there may be unexplained complaints suggestive of biliary-tract dysfunction, weakness, faintness, fatigue, indigestion, gas, distention, alternating constipation and diarrhea, heartburn, nausea with or without vomiting, and rectal pain and spasm with an occasional show of blood or mucus due to the straining. There is no relationship of the complaints to meals, the seasons, the time of day, emotional elements, or any other obvious specific factors. Therapy with one of the anticholinergic drugs results in clinical improvement in the great majority (87 per cent) of such patients.

This report is based upon a review of the records of 96 patients (49 males and 47 females) 50 years of age and over, all of whom had roentgenographic evidence of post-bulbar duodenal spasm involving the second or descending portion of the duodenum (Fig. 1). No other disorders were included.

CLINICAL FEATURES

Abdominal pain and diarrhea are the two cardinal symptoms of the post-bulbar duodenal spasm syndrome, and may occur singly or together. In this group of patients, generalized abdominal pain was found in 80 per cent (Table 1) and diarrhea in 52 per cent. Both of these symptoms occurred simultaneously in the same patient in 42 per cent of the cases.

The abdominal pain was more or less generalized. It was most commonly located between the umbilicus and the costal margins, but at times it occurred in the lower abdomen, usually just above the symphysis pubis. There seemed to be no specific localization of the pain, and it could not be made to fit into any of the classic disease entities. It did not radiate and was not referred to any of the so-called target areas. It was constantly present, varying only in intensity. There was no relationship to meals, type of food, the time of day or night, seasons, or emotional situations. Sleep was disturbed in spite of administration of various sedative drugs designed to give relief and rest.

In patients of the older age group with post-bulbar duodenal spasm, diarrhea often caused severe debilitation, with upset of the electrolyte and protein balances of the body. At times the diarrhea was almost constant, copious, watery, without odor and often without rectal sphincter control. In many cases there was almost no warning; there was an overwhelming sudden urge to have a

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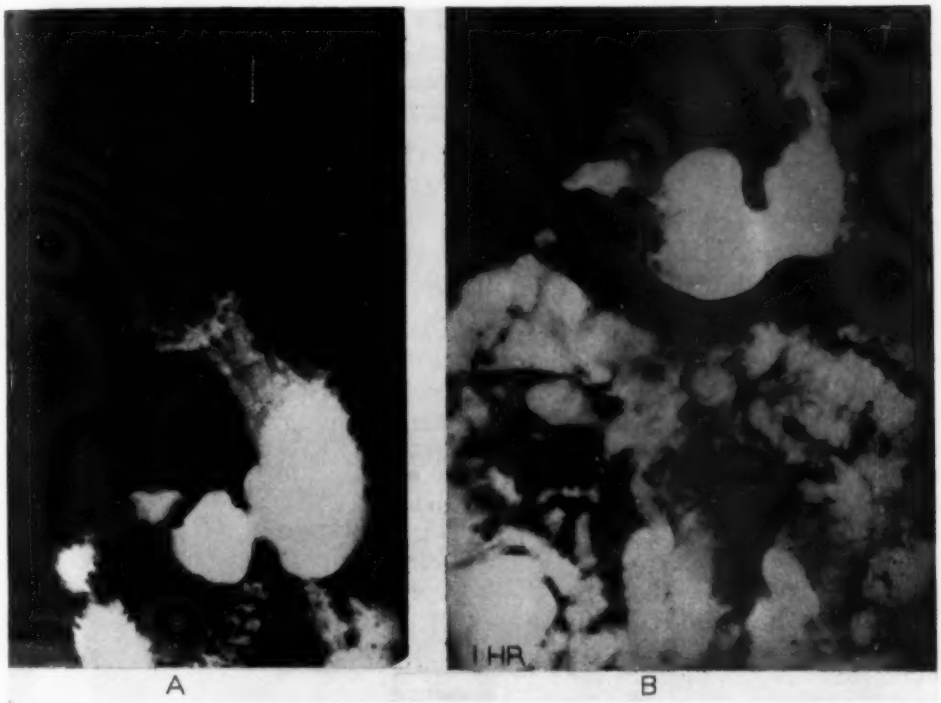

FIG. 1. Post-bulbar duodenal spasm. A. Spasm with alternate area of relaxation. B. One-hour film showing hypermotility.

bowel movement, which come on with such force that it could not be held back and the patient became badly soiled. There usually was very little, if any, straining or tenesmus. Within a relatively short time evidence of dehydration and wasting developed. The patients became exceedingly weak, listless, unable to eat or even drink fluids, and by the time they reached the hospital there was depletion of the proteins with an associated disturbance in electrolytes.

In only the rarest instances was it possible to trace from the medical history any possible exciting cause for the onset of the diarrhea. At times it seemed to be related to an upper respiratory infection treated by one or more of the antibiotics, and at other times to certain foods or drinks, but as a rule no specific cause could be found.

There were some patients in whom the bowel movements usually were thick, mushy or even semi-formed, and almost odorless, although at times they had a sweetish or even foul odor. Except in those who had violent or fulminating types of diarrhea, the average number of stools would be from 6 to 12 in twenty-four hours. As a rule, the movements occurred in a group in the morning around breakfast time, followed by a period of rest, only to recur at mealtimes or at night. Except in the severest forms, the patients usually could manage to go through the night without bowel movements. Straining and tenesmus were not common complaints, and there was usually a period of respite after each evacuation. In some instances the so-called diarrhea was actually the frequent passage

TABLE 1

Summary of Clinical Features of Post-bulbar Duodenal Spasm Syndrome in 96 Elderly Patients

	Number of Patients	Per Cent
Total	96	100
Major symptoms		
Abdominal pain and cramps	77	80
Diarrhea	50	52
Abdominal pain and diarrhea in the same patient	40	42
Symptoms suggestive of biliary-tract dysfunction (unexplained)	34	35
Additional symptoms		
Bloating, distention, gas, indigestion, rumbling	15	16
Fatigue, weakness, faintness	10	10
Constipation and/or alternating constipation and diarrhea	9	9
Nausea and/or vomiting	8	8
Rectal pain and spasm	6	7
Symptoms resembling those of duodenal ulcer	2	2
Heartburn	2	2
Headache	2	2

of fairly well-formed feces, brought on voluntarily in an attempt to relieve the abdominal pain, cramps and distress. Occasionally in those who strained to have a movement, there was a show of blood and rectal spasm and pain, which eventually caused the patient to seek relief.

Unexplained symptoms of the type associated with dysfunction of the biliary tract occurred in 35 per cent of the patients in addition to the other complaints. In 9 instances gallbladder surgery was performed, but removal of the diseased organ failed to alter the clinical picture associated with the post-bulbar duodenal spasm. Gallbladder x-ray studies were made in 67 of the patients. There was satisfactory visualization in 74 per cent, but adequate emptying in only 36 per cent. Delayed or poor emptying, even after two fatty meals, was observed in 64 per cent.

In 16 patients cholecystectomy had been performed at some previous time and these records were reviewed to determine if there was any apparent relationship between the clinical syndrome of post-bulbar duodenal spasm and the previous operative procedure. Of the 16 in this group, 14 had abdominal pain and 10 complained of diarrhea. Abdominal pain and diarrhea occurred simultaneously in 8 persons, with unexplained symptoms suggestive of biliary-tract dysfunction in 3. Gas, distention and swelling of the abdomen were found in 6, and rectal pain, spasm, blood and mucus in 3. The other complaints were fatigue, weakness, faintness, nausea (with or without vomiting), tenderness on the left side, and constipation.

Intravenous cholangiographic studies were made in 12 patients. In 4 of these the diameter of the extrahepatic biliary ducts was 8 mm. or less, whereas in 6

the diameter of the ducts ranged from 9 or 10 mm. to 25 mm. A retained stump of cystic duct was found in 2 persons, and a stone in the retained stump in another. In the patient who had a common duct 25 mm. in diameter, exploratory operation revealed only an edematous, inflamed second portion of duodenum with no evidence of malignancy, either at the head of the pancreas, the sphincter of Oddi or the common duct itself (which also was explored).

The group of post-cholecystectomy patients is too small to allow for percentage studies, but in general the clinical features were in a relationship similar to that in the whole group. Many had previously been classified as having the vague so-called post-cholecystectomy syndrome, but in reality the only positive objective finding was spasm of the second portion of the duodenum in the post-bulbar area, except in those who also had a stone or a stump of cystic duct. Previous cholecystectomy did not seem to have any significant relationship to the clinical syndrome of post-bulbar duodenal spasm.

PHYSICAL FINDINGS

Lack of definite objective findings was the most outstanding feature of the physical examination. Even in patients with marked and serious complaints, the abdomen was usually soft and relaxed; there was no evidence of peritoneal irritation and only slight, if real, tenderness just to the right or left of the midline, either high up in the epigastrium or just above the umbilicus. Patients in whom diarrhea had been prolonged and very severe manifested dehydration and, in some instances, wasting of the tissues. Occasionally some of the patients were so thin that the entire abdomen could be palpated, including the vertebral column and aorta, but no masses or other abnormalities were found.

Rectal examination frequently revealed a completely relaxed sphincter without any muscle tone, and a protruding mass of everted rectal mucosa. When the latter was replaced, the area appeared normal, except for the marked relaxation and wasting of the tissues. There was no evidence of tumors or hemorrhoids.

Sigmoidoscopy was easily accomplished in these cases because of the lack of sphincter tone, but more than usual care had to be exercised, because in this type of patient there is an increased likelihood of perforation. The sigmoidoscope was always passed under direct vision. The rectal and sigmoid mucosae were usually soft, velvety, pale pink and entirely normal. Only occasionally was slight congestion or edema observed, and in no case was there evidence of tumors, polyps or ulcerations. In patients having severe diarrhea, no special preparation for sigmoidoscopy was made; but in order to obtain good visualization of the mucosa any bits of fecal matter were washed away through the sigmoidoscope with a long cannula and syringe.

Barium x-ray examinations of the colon did not reveal any evidence of polyps, tumors, diverticula, ulcerations, or other pathologic changes in the large bowel.

DIAGNOSIS

The diagnosis of post-bulbar duodenal spasm can be made and confirmed only by study of x-ray films of the upper gastro-intestinal tract. Fluoroscopy is usually

not sufficient, and the condition may be missed unless an adequate number of films are made in various positions.

The appearance of the post-bulbar duodenal area is in marked contrast to the appearance of the relaxed and normal cap. The descending duodenum may be completely obliterated by the spasm, or may appear as an irregular, shaggy line, varying in thickness from the diameter of a thin string to that of a small-size hemp rope (Fig. 2). There may be an appearance of stiffness, and there is usually a sharp demarcation between the duodenal bulb above and the third portion of the duodenum distally. In some instances there are variable areas of spasm and relaxation in films made at different times during the x-ray examination, and in some of these the duodenal mucosa appears coarse and thick, with suggestive evidence of the edema and inflammation characteristic of duodenitis. The commonly observed relaxation at the angle of the junction of the third portion of the duodenum is in marked contrast to the spasm of the descending duodenum.

In addition to the duodenal spasm, there is frequently evidence of hypermotility, segmentation and spasm of the rest of the small intestine (Fig. 3). The barium often will traverse the entire small bowel in a matter of minutes with the cold-saline technique or by the end of the first hour using the standard method of examination, and the colon as far as the splenic flexure may be visualized.

Confirmation of the presence of post-bulbar duodenal spasm was accomplished in this study by the use of one of the anticholinergic drugs, which caused relaxation of the entire post-bulbar area and inhibition of the hypermotility in the

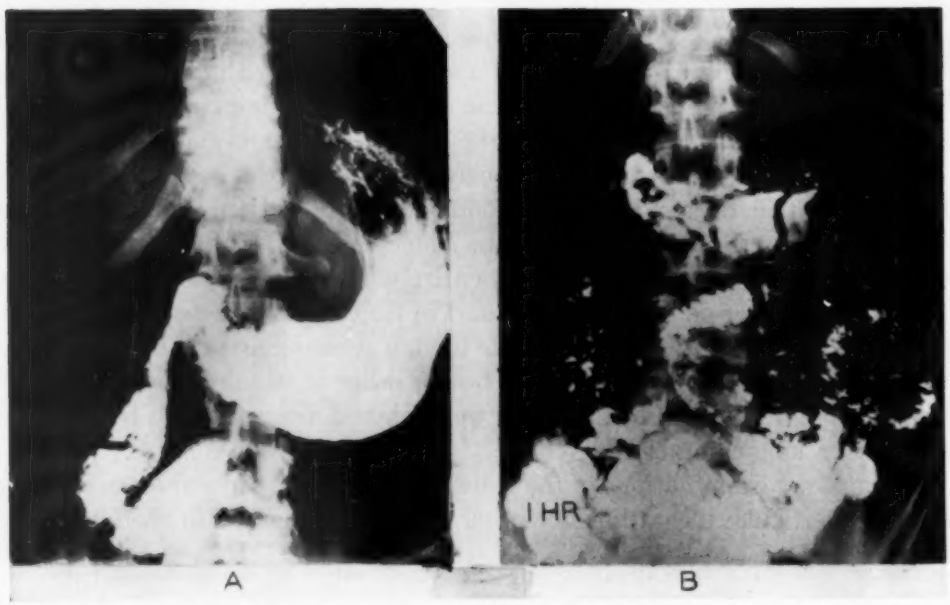

FIG. 2. Post-bulbar duodenal spasm. A. Rigidity of the second portion of the duodenum. B. One-hour film showing hypermotility, spasm, and segmentation of loops of small bowel.

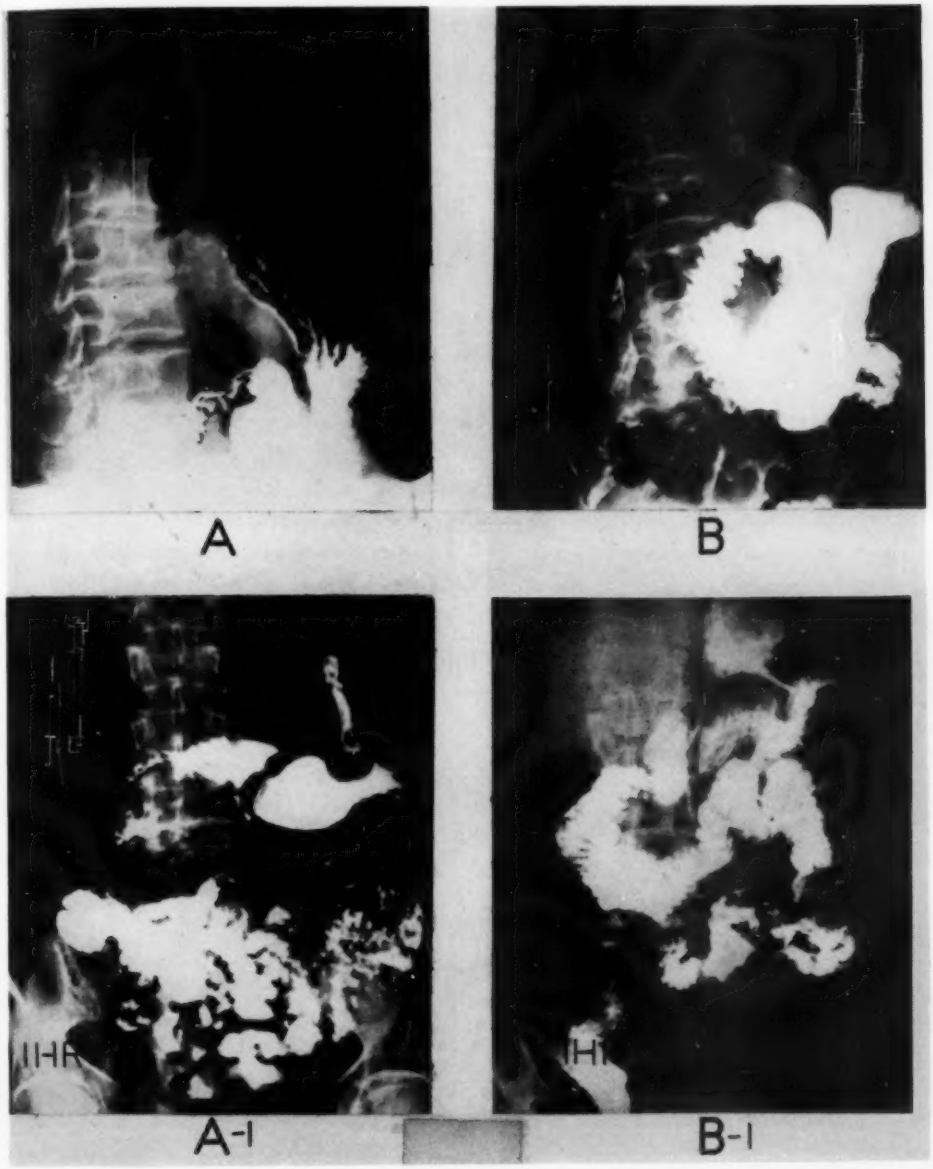

FIG. 3. Post-bulbar duodenal spasm. A. Marked spasm of post-bulbar area. A-1. Spasm and hypermotility of small bowel. B. Duodenum following administration of Pro-Banthine, showing relaxation of post-bulbar spasm. B-1. One-hour film after administration of Pro-Banthine, showing inhibition of hypermotility, and relaxation of small bowel.

small intestine (Figs. 3 and 4). Following administration of the drug, relaxation took the place of stiffness and spasm, and the mucosal pattern could then be carefully studied. The duodenal mucosa under these conditions appeared as smoothly-rounded ridges of varying height and breadth—in some instances almost pseudopolypoid-like and having a hobnail appearance. This was particularly true in patients with severe symptomatology in whom the condition had

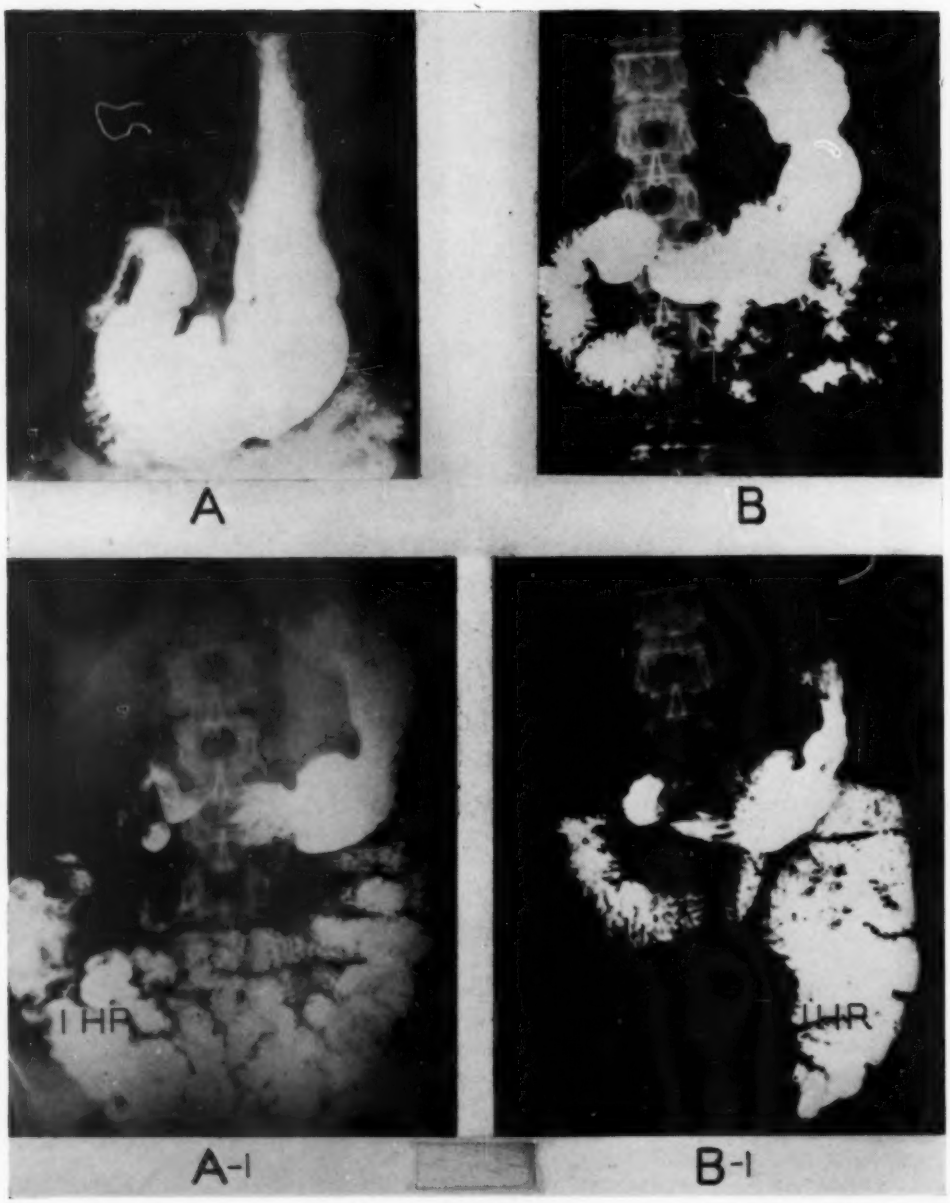

FIG. 4. Post-bulbar spasm. A. Post-bulbar duodenal spasm and rigidity. A-1. One-hour film showing post-bulbar duodenal spasm and hypermotility of small bowel. B. Duodenum after administration of Sch-2868 bromide, showing relaxation of post-bulbar duodenal spasm. B-1. One-hour film after administration of Sch-2868 bromide, showing inhibition of hypermotility, and relaxation of small bowel.

been present for a long time. Inhibition of hypermotility began in the duodenum and could be observed on the serial x-ray films to include the entire small bowel. The greatest inhibition of motility was in the jejunum, where a characteristic relaxation was seen. In some instances the barium was held in the small bowel up to seven hours. These findings explain the beneficial effects of anticholinergic drugs in the therapy of post-bulbar duodenal spasm.

TREATMENT

The two basic therapeutic indications are relaxation of spasm, and general support of the patient by means of food, fluids, electrolytes, and even blood transfusion when indicated. It is fundamentally good practice to carry on both programs of treatment simultaneously, since they are mutually dependent for the relief and cure of the patient. In most instances it is possible to carry out treatment on an ambulatory basis. When there has been severe wasting, dehydration and loss of weight, the situation becomes a medical emergency and hospitalization is required.

In order to secure relaxation of the post-bulbar duodenal spasm in patients of the older age group, either propantheline bromide, tincture of belladonna, or a newly synthesized anticholinergic, Sch-2868 bromide, was administered. In anticipation of the use of a anticholinergic, careful inquiry must be made of each patient to be sure there is no tendency to glaucoma. In an older person any one of this group of drugs could precipitate an acute attack. The other problem involved with this type of medication is that of urinary control, especially in older men with an enlarged prostate. Following a large dosage of either propantheline bromide or Sch-2868 bromide, there are times when these patients will have difficulty in starting the stream, or there may even be a mild temporary retention of urine, which is usually relieved spontaneously after about four to six hours. Future dosages then should be reduced.

In a previous study (1), it was shown that *propantheline bromide* (Pro-Banthine®) caused definite relaxation of post-bulbar duodenal spasm in 95 per cent of 73 patients in whom controlled roentgenologic observations were made before and after administration of the drug. The same medication also caused inhibition of small-bowel motility in 90 per cent of 31 patients having controlled x-ray studies. There was clinical improvement in 83 per cent of uncomplicated cases in which the drug was administered long enough to make clinical evaluation possible.

In the present investigation of the older age group, 46 patients were given propantheline bromide; in 87 per cent of these there was clinical improvement. The usual starting oral dosage was 15 or 30 mg. three times daily after or with meals, and at bedtime. If this amount did not provide relief of symptoms, the dosage was occasionally increased to 45 mg. at bedtime in addition to the 30 mg. with meals. In patients who were vomiting and required hospitalization, the initial dosage was 5 or 10 mg. intramuscularly, depending upon the weight of the patient. Because of restlessness in these cases, dimenhydrinate (Dramamine®) or diphenhydramine (Benadryl®) was given either by intramuscular injection or added to the infusion. In patients requiring hospitalization, the injections of propantheline bromide (5 mg. or 10 mg.) usually had to be repeated every six to eight hours during the period of nausea and vomiting associated with the diarrhea and resulting dehydration. It was noted, however, that following an adequate dosage of propantheline bromide intramuscularly, there was prompt inhibition of the diarrhea, and many patients would not have a bowel movement for several hours until the effect of the drug wore off. As a result,

the problems of fluid and electrolyte balances were more easily stabilized. As a rule, the intensive emergency forms of treatment were not required for more than one or two days, after which oral therapy was adequate.

A newly synthesized anticholinergic agent, *Sch-2868 bromide*, was recently reported by McHardy and his co-workers (2) as having definite inhibitory influence on small-bowel motility. A review of their report reveals that in the case illustrated, the clinical history and the roentgenologic findings were typical of those described for the post-bulbar duodenal spasm syndrome (1) in the 40-year age group. In the control x-ray films presented by these authors, there was definite evidence of post-bulbar duodenal spasm, and the barium reached the caecum in ninety minutes. Following administration of 50 mg. of Sch-2868 bromide, the films showed some relaxation of the post-bulbar spasm, but inhibition of small-bowel motility was so marked that it took six hours for the barium to reach the caecum.

Sch-2868 bromide has been available for the current investigation for only a relatively short period of time in both older and younger patients. Results of roentgenologic studies to date confirm those of McHardy *et al.* (2); and, clinically, inhibition of diarrhea has been observed. The dosage used in the older age group was, on the average, 25 mg. three times daily with meals and at bedtime. In some cases it was necessary to give 50 mg. at bedtime; in others, a dosage of one 25-mg. tablet in the morning before or with breakfast and 50 mg. at bedtime was adequate. An observation of interest is that several patients required a 25-mg. tablet in the middle or late afternoon in order to avoid a diarrheal episode during the last hour of work or early evening. The control of diarrhea seemed to be more definite than the relief of pain. A relatively small dosage of the drug would stop the diarrhea, but larger amounts were required for pain. To date, the only side-effects have been dryness of the mouth, slight blurring of vision and, in one old gentleman, slowing of the urinary stream.

Belladonna in combination with phenobarbital was used with good results in an elderly patient who was markedly dehydrated, very apprehensive, and nervous. In another older patient in whom constipation was the important symptom in addition to abdominal pain, tincture of belladonna and bismuth subnitrate (not subcarbonate or subgallate) were used, and complete relief of symptoms was obtained. The tincture of belladonna was given to the point of tolerance. The bismuth subnitrate was administered in a dosage of 1 heaping teaspoonful of the dry powder by mouth washed down with some water, three times daily before meals and at bedtime. It is important to warn the patient that the stools will become black due to the bismuth subnitrate. The use of the latter drug stems from the work of James in the early 1920's, in which he showed that administration of these dosages of bismuth subnitrate following an episode of amebic dysentery prevented development of chronic constipation and often relieved pre-existing spastic constipation. The author has used bismuth subnitrate for this purpose since 1925 in both Korea and America, with consistent results. No rationale is suggested, unless it be the relaxing effect of the nitrate factor in the preparation.

Patients who were severely ill with violent diarrhea, dehydration, wasting, pain, nausea and vomiting were hospitalized, and emergency supportive measures were applied immediately. The laboratory studies, including blood count, hematocrit and determination of blood levels of electrolytes, proteins and CO_2, were carried out as soon as possible. While waiting for the results, infusions of 5 per cent glucose in physiologic saline were administered. Multiple vitamins were sometimes added to the infusions, and Benadryl® or Dramamine® given intramuscularly for restlessness. The ingredients of the infusions should be adjusted day by day, depending upon the results of repeated laboratory determinations for essential data. It was often necessary to give transfusions of whole blood. When only protein and electrolyte adjustments were required, blood-bank plasma which had stood for at least six months was used. Intravenous supportive therapy was carried on until the patient was restored to chemical balance and able to retain adequate foods and fluids by mouth.

In many of the older patients with severe wasting and dehydration, it was found that whole adrenal cortical extract (usually in the form of Eschatin®) was of great value as an aid to stabilization. As much as 5 or 10 cc. daily could be added to the infusions. After infusions were not needed, intravenous injections of multiple vitamins and of whole adrenal cortical extract (5 cc.) were given daily. Administration could usually be accomplished by preparing the material in two separate syringes and using one needle for the injection.

The use of opiates was avoided and found to be unnecessary, even though many patients had previously taken these drugs for varying periods of time before being seen. For sedation, either Dramamine® or Benadryl® was administered when indicated, along with each dosage of anticholinergic or only at night for inducing sleep.

When patients could accept food by mouth, they were urged to eat a high-protein, high-caloric diet, with an adequate supply of fresh fruits and vegetables. Many had literally starved themselves by eliminating one food after the other in the belief that some article of diet might be causing their trouble. Great patience was often needed in developing the patient's confidence and re-educating him to eat a full, well-balanced diet.

In some persons who needed intravenous therapy but could not readily be hospitalized, the infusions were given as an office procedure. These patients were required to rest for an hour or two afterward before going home. Intravenous infusion is also a practical measure for the home in selected instances, but it is better carried out in the office under careful supervision.

In the older patients, the secondary side-effects of the anticholinergic drugs had to be watched for diligently and proper measures instituted when necessary. Any tendency to glaucoma became a positive contraindication to such therapy, but simple blurring of vision or dryness of the mouth could be counteracted by alteration and spacing of the dosages. It was found that giving the drug once or twice daily in an amount adequate to control the symptoms was far better for the patient than giving many small, ineffectual amounts scattered throughout the day. Difficulty in urination, in both males and females, was not infrequent as a

complication and at times was rather bothersome. In the patients in whom adequate dosage of the anticholinergic was required for relief of the gastro-intestinal symptoms, the urinary problem was controlled either by spacing the medicine or by simultaneously giving a dosage of bethanechol (Urecholine®). Even though bethanechol is a pharmacologic antagonist of the anticholinergics, by properly gauging the dosages of each type of drug the desired relief of both gastro-intestinal and urinary symptoms could be achieved. The main requirement was careful, close observation of the patient, with alteration of the dosage of each drug until proper balance was obtained. When the patient became convalescent from the gastro-intestinal disturbances, the anticholinergic drug was reduced in amount and the complications subsided. Adequate sedation was usually accomplished by either Dramamine®, Benadryl®, chloral hydrate, or the bromides. Only on the rarest occasion was it found necessary to give one of the barbiturates, and never any of the opiates.

Psychotherapy had no place in the program of therapy, as there was no indication for it.

SUMMARY AND CONCLUSIONS

1. The records of 96 patients 50 years of age and over with roentgenologic evidence of post-bulbar duodenal spasm have been reviewed.

2. The clinical syndrome of gastro-intestinal invalidism without specificity apparently resulting from the post-bulbar duodenal spasm, is characterized by generalized abdominal pain or diarrhea or both, by unexplained symptoms typical of biliary-tract disorders, and by a group of distressing and often debilitating symptoms such as bloating, distention, gas, weakness, fatigue and faintness. Even though the latter symptoms were not as commonly complained of as some others, they were of greatest importance in individual cases. In older patients the diarrhea was often severe and accompanied by dehydration, debilitation and wasting. There were also coincident disturbances of protein and electrolyte balances.

3. Results of physical examination were essentially negative, as were the results of sigmoidoscopy and barium x-ray studies of the colon.

4. Diagnosis was made by means of x-ray film studies of the upper gastro-intestinal tract. These showed spasm of the second portion of the duodenum in the post-bulbar area. The diagnosis of spasm in this area was confirmed by re-examination after administration of an anticholinergic drug; the x-ray film then revealed relaxation of the spasm and evidence of edema, swelling and thickening of the duodenal mucosa. Hypermotility and spasm of the small intestine were also observed during the diagnostic x-ray studies, but following administration of an anticholinergic there was inhibition of hypermotility and relaxation of spasm.

5. Specific therapy was aimed at obtaining relaxation of the post-bulbar duodenal spasm by means of propantheline bromide, belladonna, or a newly synthesized anticholinergic, Sch-2868 bromide. The latter two drugs were not used in a sufficiently large number of patients to make possible an accurate statement

of results. The data on the effects of Sch-2868 bromide indicate a significant degree of relaxation of post-bulbar duodenal spasm, and definite inhibition of hypermotility of the small bowel. The clinical results with Sch-2868 in the control of diarrhea were most gratifying, but observation of still larger numbers of patients over a prolonged period of time is necessary for accurate evaluation of the drug. In the case of propantheline bromide (Pro-Banthine®), there was improvement in 40 out of 46 patients who received it for periods of time long enough to warrant therapeutic evaluation. No serious side-effects were observed, although these frequently became a nuisance to the patient. The major therapeutic problem was to determine clinically the dosage necessary to provide relief of symptoms. The main cause for failure was inadequacy of dosage. No toxic or cumulative effects were observed even after prolonged therapy. In contrast with the customary use of opiates in the past for the treatment of this condition, it was not necessary to use opiates in any form in this series of patients.

6. General supportive therapy was administered in association with the specific medications. Infusions of fluids, electrolytes, proteins, or even blood were given when indicated.

7. A full, unrestricted diet (except for alcohol in any form) was used in all cases.

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AGE AND ANESTHESIA

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The choice of anesthesia for the geriatric patient should be based upon physical status. Chronologic age, as a rule, is no index of risk. Age may yield a clue to possible physical status, but can be misleading. Patients of advanced years are often in surprisingly good condition. The fact that they have survived so long may attest to the possession of a rigorous constitution. Occasionally middle-aged patients are seen who appear older than they are in years and who are afflicted with serious medical complications which preclude a successful outcome of a contemplated operation; yet others, who are much older, weather these procedures satisfactorily. Even though evaluations of geriatric patients are carefully made, attempting a prognosis occasionally leads to embarrassment. The patient whose physical status appears satisfactory and obviously should withstand a contemplated procedure without difficulty, may die unexpectedly from some unanticipated cause. On the other hand, a patient who appears to be an obviously poor risk and whose survival is doubtful, does surprisingly well. The element of uncertainty of the outcome in patients of advanced age has not been eliminated, in spite of diagnostic refinements.

In present-day practice, patients heretofore deemed inoperable, because of age, are scheduled for formidable procedures without hesitation. In geriatric patients, many of the diseases for which surgery is indicated require extensive operations. Resections of various organ systems which have undergone neoplastic or degenerative changes, both in the abdomen and the thorax, are attempted without trepidation. Frequently these operations are long, tedious, time-consuming, and more radical than the procedures performed in younger more vigorous subjects for diseases of a more benign nature. Thus, in selecting anesthesia for the geriatric patient it is necessary to consider not only the clinical factors peculiar to these patients but also the nature of the operation.

CLINICAL FACTORS IN ANESTHESIA

Some of the clinical factors which bear directly on the choice of anesthesia are: 1) status of the cardiovascular system, 2) status of the blood volume, 3) status of the respiratory system, 4) hepatic and renal function, 5) the nutritional state, 6) endocrine function, 7) metabolic activity, 8) changes in the skeletal system, 9) recuperative powers, and 10) the status of the nervous system. Unfortunately, derangements of these systems rarely occur singly; were it so, the problems of anesthesia and surgery in the aged would be less complex. Instead, it is common to have several systems involved simultaneously.

Most of the disorders of the cardiovascular system are characterized by loss of elasticity of the vessel walls in varying degree. Reflex adjustment to the de-

mands for increased blood flow, changes in blood pressure, loss of fluid, and alterations in blood volume do not occur as readily or as easily as they do in young patients. Coronary artery disease, arteriosclerosis and hypertension are common complications. Vascular overload from excess blood, plasma and other intravenous fluids may precipitate cardiac failure.

Chronic pulmonary diseases further enhance dysfunction of the vascular system. Particularly distressing is chronic emphysema. The patient with the so-called barrel chest, familiar to all, has lowered arterial oxygen and elevated blood carbon dioxide tension. Diaphragmatic movements are exaggerated and interfere with surgical manipulations, particularly in the upper abdomen. Chronic inflammatory diseases of the lung may be present, often accompanied by suppuration. Secretions and purulent discharge are troublesome, irrespective of the anesthetic employed. Coughing, and laryngeal and bronchial spasm may occur, particularly when spasmogenic drugs such as the thiobarbiturates (thiopental, thiamylal) are used.

Less common, but serious when present, is impaired renal function. Irrespective of the cause, whether degenerative disease of the kidney or disease of the heart or blood vessels, the balances of fluid, acid-base and electrolytes are disturbed. These abnormalities are difficult to correct, and often made worse by both anesthesia and operation. Digestive disturbances may have led to weight loss, emaciation and diminished muscle tonus. The venous system lacks the normal support of skeletal muscle, which is necessary to assist in the return of venous blood to the heart, and is an important factor in maintaining a normal cardiac output. Reduced concentration of serum protein, vitamin deficiency, or anemia may be present, all of which complicate the problems of both anesthesia and surgery. Anemia, particularly, requires correction because it is associated with diminished blood volume and decreased gas transport by the blood. Obesity, so prominent in middle-aged patients, is less prevalent in the aged, as the life expectancy of the obese is not as long as that of the young. Obese patients are poor risks from the standpoint of anesthesia because one has difficulty in maintaining an adequate airway and proper ventilation; in them, the supine position (to say nothing of the prone, lateral and head-down position) plays havoc with the ventilatory excursions. Fibrosis of the liver may be the basis of impairment of hepatic function.

The diminished tolerance of aged patients to nonvolatile drugs, particularly the narcotics and hypnotics, is partly due to the diminished activity of the detoxifying mechanisms. For this reason, prolonged somnolence and depression of the respiratory and circulatory systems are common after the use of thiobarbiturates, narcotics, tribromethanol and similar nonvolatile drugs. The pancreas may undergo fibrotic changes. Diabetes, with its disturbed metabolism and associated vascular changes, is not uncommon. Metabolic activity is reduced as the result of the changes in the endocrine glands. The metabolic rate declines gradually after the middle forties. Decreased metabolic rate and decreased tolerance to narcotics and hypnotics are interrelated. Proportionately smaller doses of these drugs are required in older persons compared to the young

or middle-aged adults, both for pre-anesthetic medication and postoperative sedation and relief of pain.

When there is sclerosis of the cerebral vessels, there may be mental symptoms and a reduction in reflex activity. Behavior problems caused by senility may seriously interfere with the proper care of the patient in both the preoperative and postoperative periods. Narcotics and hypnotics often enhance psychic disturbances and cause excitement instead of sedation.

As age advances, the skeletal system invariably undergoes progressive alterations, *e.g.*, deformities, degenerative changes and arthritic processes in the bones and joints. Fusion of the vertebrae often interferes with flexion and extension of the spine. Thus, proper positioning on the operating table, hyperextension of the head for proper maintenance of the airway during general anesthesia, flexion of the neck for intratracheal intubation, and procedures such as lumbar puncture are often impossible.

Many patients are edentulous. In them, it is difficult to apply a mask to the face for induction of inhalation anesthesia, and therefore a completely closed system cannot always be established unless intratracheal intubation is used. The edentulous patient, however, is easily intubated.

The recuperative powers of the aged are often diminished. Healing of wounds may be delayed, and the convalescent period is usually longer than in younger subjects. Pulmonary complications and thrombo-embolic phenomena may result from enforced confinement in bed.

SELECTION OF ANESTHETICS

For anesthesia, drugs which cause generalized listlessness, and inactivity are undesirable; techniques which assure rapid recovery are preferred. In the aged, early ambulation is often practiced in order to avoid postoperative circulatory and respiratory complications, and anesthesia must be selected with this in mind. Doses of analgesics and hypnotics should be reduced to quantities which do not cause respiratory depression and inactivity in the postoperative period. For this reason the combinations of drugs so commonly used in present-day anesthesia practice seem undesirable and should be replaced by techniques embodying the use of single agents.

Age per se is no contraindication to the use of any anesthetic drug. The statement is often heard that this drug or that drug cannot be used for old patients. Emphasis is placed upon the age instead of the existing pathologic entity which contraindicates the use of the drug and upon the type of anesthesia required in order to provide proper operating conditions.

Nitrous oxide or ethylene, for example, rarely yields satisfactory surgical anesthesia in young and vigorous patients, unless there is some degree of anoxia, or some other drug is used in combination. In aged patients, on the other hand, relaxation without anoxia is frequently obtained with these anesthetics. There are no contraindications to the use of nitrous oxide and ethylene in elderly patients, provided oxygen tension is adequate. When this requirements cannot be fulfilled, other volatile anesthetics may be added, and fractional doses of

basal hypnotics such as the thiobarbiturates (*e.g.*, pentothal or thiamylal) may be used as adjuncts.

Cyclopropane, in the absence of serious cardiovascular disease, not only is suitable, but desirable for the aged, because it is labile and permits lightening and deepening of anesthesia at will. In addition, the administration of high concentrations of oxygen can be assured and moderate degrees of muscle relaxation are easily obtained. No serious physiologic or metabolic disturbances follow its use. The statement that cyclopropane cannot be used in the aged has no scientific basis. The more conservative anesthetists avoid the use of cyclopropane when cardiovascular diseases are present. Since cardiovascular diseases are frequent medical complications in older persons, opportunities for using cyclopropane may be less in aged patients than in younger ones. Instead of carrying the administration of cyclopropane to the deeper levels of anesthesia, succinyl choline may be used to obtain muscle relaxation.

Objections are often raised to the use of *ether* in the aged. The most valid objection to ether is the slow recovery and the prolonged period of somnolence which invariably follows. Since early ambulation is desirable, ether is a drawback in this respect. Nausea, vomiting and general discomfort occur more frequently after ether, and restrict the patient's activity for a longer time in the immediate postoperative period. Ether enhances existing acidosis to a greater extent than other currently used inhalation anesthetics.

The *combination of cyclopropane and ether* is used extensively by some anesthetists. In many ways it is an ideal combination for major surgical procedures. The induction of anesthesia is made rapid and pleasant with cyclopropane, and the struggling, excitement, spasm and other disagreeable characteristics of the induction of ether anesthesia are avoided. Ether is then added gradually. Thus, the quantity of each drug is reduced proportionately. Cardiac disturbances, even in those who have diseased hearts, rarely develop during light cyclopropane anesthesia. Should they develop, they disappear as soon as ether is added. Ether also reflexly increases ventilation, thus averting the respiratory depression so characteristic of cyclopropane anesthesia. Considerable discussion is heard concerning the diminished ventilation accompanying most forms of general anesthesia. Assisted, controlled respiration is advocated to compensate for this hypoventilation. Controlled respiration is artificial respiration. The word artificial is well selected because it describes exactly what is accomplished when it is applied to respiration. When voluntary respiratory efforts are made, a negative intrathoracic pressure develops which serves the dual purpose of drawing air into the lungs and facilitating the return of venous blood to the heart. Failure to maintain an adequate venous return ultimately results in a decrease in cardiac output. Most recommended methods of artificial respiration rely upon developing a positive intrathoracic pressure for pulmonary filling. Thus, irrespective of the method employed for controlled respiration (whether mechanical or manual), ventilation differs from normal breathing. No method of artificial respiration accomplishes ventilation as effectively as the patient's voluntary efforts. Ether is the only currently used major general anesthetic which does not cause some

degree of hypoventilation. Minute volume exchange is normal or increased and the patient can accomplish adequate ventilation voluntarily.

Other inhalation anesthetics, such as vinyl ether, Vinamar, ethyl chloride and chloroform are seldom used in present-day practice. They certainly have no place in surgery of the aged. Trichlorethylene may be used as an analgesic for minor surgical procedures, but not for surgical anesthesia. It is often employed (using a semi-closed device known as the Cyprane Inhaler) for painful manipulations such as the removal of dressings, application of casts, skin grafting and other procedures which can be performed without loss of reflex activity.

Nonvolatile drugs, such as tribromoethanol (Avertin), paraldehyde, thiopental and similar ultra short-acting barbiturates should be avoided as much as possible. They may cause prolonged depression, particularly when used in excess. Thiopental, hexobarbital (Evipal) and thiamylal (Swital) are unsatisfactory as sole anesthetic agents. They should be combined with a drug which is analgesic, such as nitrous oxide, because they lack analgesic properties of their own. The quantity of barbiturate should be kept at a minimum. Muscle relaxants may be used with caution. They should not be given to the point of apnea. Overdosage may result in prolonged apnea in the postoperative period—a troublesome complication. The tissues of most aged people are usually relaxed, and deep anesthesia or muscle relaxants are not necessary. When the latter are indicated, succinyl choline is preferred because it has an evanescent action due to its rapid hydrolysis. Greater control and more rapid recovery are permitted by the use of this drug.

Regional anesthesia serves admirably in many situations for surgery in the aged. The deep-rooted impression that local anesthesia is the best when dealing with poor-risk patients is not necessarily correct. Certain operations cannot be performed properly with local anesthesia, irrespective of the skill of the operator. There are many instances in which local anesthesia could be used if the operator were gentle; but as this is not always the case, it is not suitable for all operators. There are other instances in which the available technique for induction does not supply adequate anesthesia for a contemplated procedure, irrespective of the skill of the anesthetist. In such instances, many operators resort to the infiltration techniques and succeed in obtaining anesthesia after using quantities of the anesthetic drug far above the safe limit, or after employing a variety of intravenous hypnotics and narcotics and ultimately inhalation anesthesia to complete the procedure. Whenever possible, field blocks are preferable to local infiltration; anesthesia is extensive and complete, and the total quantity of drug used is much less than that required for infiltration. It must be remembered that the aged do not tolerate large quantities of local anesthetic drugs as well as do younger adults. Aged persons do not detoxify the drugs as readily and as easily. Moreover, local anesthetics depress the heart and reduce cardiac output, particularly if cardiac disease exists. Hypotension is not uncommon when excessive quantities of local anesthetics are injected.

Among the useful *nerve blocks* are brachial plexus block for operations on the upper extremity, cervical plexus block for operations of the neck, lower inter-

costal nerve blocks or abdominal field block for abdominal surgery, and combined femoral and sciatic block for procedures on the lower extremity. The use of epinephrine in combination with a local anesthetic for operations on the toes, fingers and other appendages is not safe practice. Gangrene may occur, particularly if peripheral vascular disease is present.

Spinal anesthesia is ideal when there is no absolute contraindication to its use. As a rule, low spinal anesthesia is tolerated reasonably well even by patients who have mild impairment of the cardiovascular system. Obvious and serious cardiovascular disease is almost an absolute contraindication to spinal anesthesia—certainly for high spinal anesthesia. The aged do not tolerate circulatory derangements caused by this procedure as well as do young subjects. The hypotension which occurs in subjects of all ages during spinal anesthesia is usually more abrupt in onset, more severe, and more difficult to control in the aged. Vasopressor drugs are not always as effective in the aged as in young adults; the response may be fleeting and not sustained. Obviously, when the circulatory system is impaired in any manner, an anesthetic procedure which precipitates circulatory derangements (*e.g.*, spinal anesthesia) is best avoided. Hypotension is more severe and more difficult to reverse in cases of cardiovascular disease, anemia, shock or dehydration. Sympathectomized subjects do not tolerate even mild degrees of hemorrhage. Spinal anesthesia is best avoided when bleeding is anticipated, unless provisions are made for immediate adequate blood replacement. In cases of increased intra-abdominal tension from ascites, intestinal obstruction, marked gaseous distention, or tumor masses of unusual size, severe hypotension develops promptly after induction of spinal anesthesia, and it is often difficult to reverse or control. The mechanisms causing it are not understood; most likely, compression of the great veins in the abdomen interferes with the return of venous blood from the extremities to the heart. The aged, in whom many of these complicating factors exist, are usually not good subjects for spinal anesthesia.

Abstracts of Current Literature

PRIME ESPERIENZE CLINICHE CON UNA NUOVA SOSTANZA PSICOMIMETICA (CLINICAL EXPERIENCE WITH A NEW "PSYCHOMIMETIC" SUBSTANCE).

Alema, G., and Sergio, C. *Riv. sper. freniatr.* (It.) **80:** 989, 1956; through Ciba Literature Review **2:** 88 (March) 1957.

The intravenous injection of 20 mg. of Ritalin facilitates diagnosis in various mental diseases. This test was applied to 41 patients suffering from different kinds of neuroses, schizophrenia, delirious states or depression. An abreaction was produced more frequently with Ritalin than with psychomotor amines, and the basic symptoms were also more easily recognizable. In many cases, this method enabled an exact diagnosis to be made. The effect of Ritalin commences more quickly and also disappears sooner than that of a psychomotor amine injected in a corresponding dose. After approximately two hours the patient is again, generally speaking, the same as he was before the injection. For this reason, the drug is particularly suitable for ambulatory patients. There is no danger of insomnia, if the Ritalin test is performed in the morning. The euphoristic effect of Ritalin is less pronounced than that of the psychomotor amines, and the dejection which frequently occurs the day following the use of these drugs is much less marked, or absent, after Ritalin. Ritalin has little effect on the autonomic nervous system, with the result that this test is more pleasant for the patients. There need be no fear of undesirable reactions.

SYSTEMIC MANIFESTATIONS OF HYPERNEPHROMA. A REVIEW OF 273 CASES.

Berger, L., and Sinkoff, M. W. *Am. J. Med.* **22:** 791 (May) 1957.

The fact that in a significant number of cases of hypernephroma no classic local manifestations are present at the onset of the disease poses a serious challenge in differential diagnosis. Two hundred and seventy-two proved cases of hypernephroma are reviewed in order to elucidate the systemic manifestations of the tumor and point out the need for greater suspicion in its diagnosis. There were approximately twice as many men as women in the group, and an 81 per cent incidence of the disease after the age of 50 years. The incidence of the usual signs and symptoms, in terms of percentage of patients involved, was as follows: flank pain, 42; gross hematuria, 18; weight loss, 31; fever, 16; palpable mass, 63; and anemia, 28. Findings compatible with renal tumor were present in 252 patients in whom urography was performed. The "nonurologic" signs, symptoms or complaints, with percentile incidence, were: fever of undetermined origin, 2.5; amyloidosis, 3; absence of hematuria, 44; signs of debility as the sole manifestation, 1.8; polycythemia, 1.8; misdiagnosed abdominal mass, 3.6; metastasis fourteen years after nephrectomy for original tumor, 0.4; presenting complaint pulmonary, 3.6; presenting complaint osseous, 3.0; and presenting complaint neurologic, 1.8. The difficulties encountered in diagnosis when several of these signs and symptoms are present are discussed and the pertinent literature reviewed. An awareness of the protean manifestations of hypernephroma should aid in its diagnosis.

RHEUMATIC CARDITIS IN LATE ADULT LIFE.

Caputi, A. *Rhode Island M. J.* **40:** 160 (March) 1957.

Three cases of rheumatic carditis in the older age group are presented in order to reaffirm the necessity of considering underlying rheumatic carditis in bizarre manifestations

of heart disease, but especially to emphasize that underlying atherosclerotic or inactive rheumatic heart disease itself may confuse the clinical picture. Electrocardiograms may not help in the diagnosis because of camouflaging or nonspecific patterns. Tachycardia and cardiomegaly may be due to an old cardiac pathologic condition and not to active carditis. It is important to consider underlying active rheumatic carditis in all types of active or suspected heart disease. Diagnosis may be difficult, but may be aided by repeated determination of O-antistreptolysin titers. The recent advances in prevention of the rheumatic state by the use of penicillin, and the ameliorating effect of the corticosteroids, accentuate the need for developing more accurate diagnostic tests. A high index of correlative clinical suspicion, however, will continue to be of great value. (From author's conclusions and summary.)

LES ÉPANCHEMENTS HÉMORRAGIQUES DES CIRRHOTIQUES (THE HEMORRHAGIC EFFUSIONS ASSOCIATED WITH CIRRHOSIS OF THE LIVER).

Cattan, R., and Vesin, P. *Sem. hôp. Paris* **33:** 80, 1957; through Ciba Literature Review **2:** 81 (March) 1957.

A fairly rare complication observed in patients with cirrhosis of the liver due to alcoholism is that of hemorrhagic effusions in the pleural or peritoneal cavity. In such cases, the coagulation and bleeding times are normal and the prothrombin content, although reduced, is still well above the danger level. These effusions are transudates, since the protein content of the fluid is always less than 2 per cent. Nevertheless, they differ from ordinary transudate in two respects: the albumin level is somewhat higher than normal (1.5 to 2 per cent instead of 1 to 1.5 per cent); and the fluid is rich in white and, above all, red, blood corpuscles. The effusions of cirrhotic patients are always associated with the formation of edema. Presumably, they are due to the fact that the capillaries in the abdominal cavity or the mediastinum are injured in the same way as when edema develops, but to a greater extent. The occurrence of such a lesion might be accounted for by a sudden rise in venous pressure in the region concerned or by the release of toxic substances from the blood vessels. These effusions are not necessarily to be regarded a sign of ill omen for the patient. Administration of prednisone has produced favorable results, although it is not always possible to prevent a fatal outcome.

CERVICAL METASTASIS FROM OCCULT CARCINOMA.

Comess, M. S.; Beahrs, O. H., and Dockerty, M. B. *Surg., Gynec. & Obst.* **104:** 607 (May) 1957.

This paper is an abridgment of a portion of a thesis. Among 1,189 patients with metastatic carcinoma in the cervical lymph nodes, the primary tumor could not be found initially in 103 (9 per cent). The latter group forms the basis of this study. Approximately 75 per cent of these patients were between the ages of 40 and 70 years. The primary tumor was found subsequently in 42 patients (Group I); 16 patients had no further evidence of malignant disease (Group II); 42 patients died without the source of metastasis having been discovered (Group III); and 3 patients were lost to follow-up. Among Group I patients, the thyroid gland was the site of the largest number of cryptic primary lesions, followed by the nasopharynx and tonsil as the next most frequent sites. Each of the patients in Group II had an epithelial tumor in the soft tissues of the neck without subsequent evidence of a primary carcinoma. These were squamous-cell or indeterminate neoplasms except for one which was a Grade 2 adenocarcinoma in a middle deep cervical node. These patients were treated as follows: local excision, 1; dissection of lymph nodes, 6 (with radiation in 4); and radiation, 8. One patient died after four and one-half years of coronary occlusion, but the others remained well without evidence of a primary tumor for one and a half to eleven years after the initial examination. Among Group III patients, 1 died prior to examination, 39 died two weeks to thirty-six months following diagnostic evaluation, and 2

remained alive with extensive recurrent disease. Differences in survival time did not appear to be related to the pathologic aspects of the neoplasms. The pathologic type of lesion metastatic to cervical lymph nodes was of diagnostic significance. Squamous-cell carcinomas in cervical lymph nodes in general appear to originate in the head and neck. Adenocarcinomas originate in the thorax or abdomen. The location of the metastases is important in locating the site of the primary tumor. Metastasis from tumors of structures of the head and neck usually occurs to the chain of lymph nodes in the region of the primary lesion. Metastases in the lower part of the neck that are not squamous in nature probably arise from abdominal or thoracic organs. Upper cervical squamous-cell lesions usually originate in the epithelium of the oral cavity. Lymphoepitheliomatous and transitional-cell variants are likely to arise from the nasopharynx or tonsils. High-grade squamous-cell epitheliomas are likely to arise from the base of the tongue or the hypopharynx. Subglottic lesions and those from the upper esophagus are likely to metastasize to the lower portions of the cervical collar. That a few squamous-cell carcinomas may be primary in the deep tissues of the neck may be surmised from the long survival of some Group II patients without evidence of a primary source before and after treatment. Every effort should be made to secure an accurate diagnosis when the presence of metastases is proved. All indeterminate cervical masses should be explored surgically following exhaustive clinical examination, and definitive surgery should be performed then, or later, as indicated. The prognosis varies with the location and pathologic nature of the cervical tumor, which should be determined in each case.

CARCINOMA OF THE CERVICAL STUMP.

Decker, D. G.; Hunt, A. B.; Fricke, R. E., and Nelson, G. A. *Am. J. Obst. & Gynec.* **73:** 974 (May) 1957.

Ninety-eight cases of carcinoma of the cervical stump seen at the Mayo Clinic during the years 1940 through 1949 are reviewed. Eighty-four were "true" cases and 14 "coincident" cases, that is, they occurred within two years after partial hysterectomy. The malignant lesion was a squamous-cell epithelioma in 69 true cases and in 12 coincident cases, and an an adenocarcinoma in 14 cases and 1 case, respectively. There were 2 unidentified far-advanced carcinomas in each group. Most of the patients were between the ages of 40 and 60 years. Vaginal bleeding was the most common complaint, with leukorrhea second. Six patients had no symptoms; the carcinoma was discovered upon routine examination. Twenty-one patients in each group had never been pregnant or had had only 1 pregnancy. However, hysterectomy had not been performed in them until they had reached an average age of 44 years. The primary reason for subtotal hysterectomy in the entire group had been fibromyomas; the other major reasons were uncontrollable uterine bleeding and pelvic inflammatory disease. The operation was performed at an average age of 42.7 years. The average lapse of time between operation and recognition of the cancer was 11.5 years. The cancer was found in the majority of patients within five to ten years, but in a sizable number fourteen to twenty years later, and in 1 patient thirty-five years later. Eighty-one patients were treated by radium and roentgen-ray therapy in combination, 3 by roentgen-ray therapy alone, and 9 by radium therapy only. Surgery was performed in 5. Seventy-six of the true cases could be traced; 67.1 per cent of these patients survived for five years or more. Thus the salvage rate was increased over the 26.3 per cent rate in the group reported during the years 1915 through 1930. Improvement is attributed to the fact that more patients were seen relatively early in the course of the disease, increased skill in the use of radium, and the recognition of satisfactory radiation response in the tumors. All patients in the coincident group could be traced for five years or more and had a survival rate of 42.9 per cent. Total hysterectomy at the time of operation, with rare exceptions, would have avoided carcinoma in all of these. With more extensive use of the cervical smear for cytology studies and the recognition of preclinical carcinoma of the cervix, this situation will become more unusual. At present, carcinoma of the cervical stump requires the highest diagnostic skill and the most competent therapeutics.

BIOLOGICAL EFFECTS OF PHOSPHORAMIDES IN PATIENTS WITH ADVANCED CANCER.
Humphrey, E. W., and Hitchcock, C. R. *Cancer* **10:** 231 (Mar.–Apr.) 1957.

Triethylenephosphoramide (TEPA) and triethylenethiophosphoramide (TSPA) were tested for carcinolytic action in 7 and 27 patients, respectively, with far-advanced carcinoma. The location of the cancers treated with TEPA and their numbers were as follows: lung, 4; colon, 1; rectum, 1; and melanosarcoma, 1. Those treated with TSPA were: breast, 5; ovary, 4; lung, 3; melanosarcoma, 3; embryonal cancer of the testis, 2; and lymphosarcoma, Hodgkin's disease, reticulum-cell sarcoma, hypernephroma, cancer of the penis, Ewing's sarcoma, cancer of the submaxillary gland, cancer of the larynx, rhabdomyosarcoma of the buccal cavity, and malignant teratoma, 1 each. Of each drug, a dose of 10 mg. was given daily for five days, and then a smaller daily dose was administered until a total of 70 to 150 mg. had been administered. A weekly maintenance dose of 8 to 10 mg. is now being given to patients who have a good response to the larger initial doses. The effect on the tumor was judged by the decrease in size or disappearance of tumor masses or decrease in size of lymph nodes, as well as by roentgenographic evidence of improvement in lung or skeletal tissue. Significant regression of the tumor occurred in 1 patient with carcinoma of the lung treated with TEPA and in 13 patients with carcinoma of the ovary, carcinoma of the breast, Hodgkin's disease, lymphosarcoma, malignant teratoma, or malignant melanoma treated with TSPA. The regression in breast cancer without the use of hormones was considered a noteworthy accomplishment. A strong correlation was found between carcinolytic action and the occurrence of leukopenia. In the 13 patients with tumor response in the TSPA series there was severe depression of the leukocytes, whereas in only 1 of those with no tumor response did leukopenia develop while under treatment with this drug. In 4 of the 7 patients treated with TEPA, a severe degree of bone-marrow depression was noted approximately ten days after treatment was started. Because of a delay in the leukopenic response, both compounds should be initiated with caution. It is especially important to give small doses originally to patients with adenocarcinoma of the ovary because they were found to have severe leukopenia when given smaller doses of TSPA. Studies of uric-acid excretion during the administration of these drugs showed that the production of uric acid by the body is depressed for a time after treatment with TEPA in patients failing to show tumor regression, whereas marked carcinolytic action in patients treated with TSPA was accompanied by a two or threefold increase in uric-acid excretion. The agents studied are palliative in metastatic carcinoma and the investigation of their use should be continued.

BLOOD PRESSURE IN APPARENTLY HEALTHY AGED 65 TO 106 YEARS.
Master, A. M.; Lasser, R. P., and Jaffe, H. L. *Proc. Soc. Exper. Biol. & Med.* **94:** 463 (March) 1957.

Blood pressure was studied in 2,998 men and 2,759 women 65 to 106 years of age, who were apparently healthy and without known heart disease. The mean blood pressure for the men was 145/82 and for the women 156/84. Both the mean systolic and the mean diastolic pressures showed no continuous rise after age 65. In men, the average systolic pressure increased by 2 to 3 mm. in the age groups 65 to 69 and the seventies to a peak of 146 mm. In women, the increase in the systolic pressure in the same age groups was 5 mm. to a peak of 159 mm. After age 74, the systolic pressure declined slowly in women but remained practically constant in men. The average diastolic pressure in both sexes showed little variation from ages 65 to 80, and tended to decline thereafter. The average reached a maximum of 83 mm. in men at ages 65 to 69 and a maximum of 85 mm. in women at ages 65 to 74 years. Frequency distribution curves of the systolic and diastolic pressures were constructed for each sex in five-year age groups up to age 95, and one for those persons 95 years of age and over. All of the curves had a basic bell shape. In both men and women, the curves were somewhat skewed to the right, the skewness being larger and more consistent in the systolic than in the diastolic pressure. A set of blood-pressure standards was

computed for each sex, applicable to the healthy population from age 65 to over 100 years. These computations place the middle 80 per cent range (±2 sigma) in males at $\frac{115\text{–}175}{70\text{–}95}$ and in females at $\frac{120\text{–}192}{65\text{–}102}$; and the middle 95 per cent range (±2 sigma) in males at $\frac{100\text{–}190}{62\text{–}102}$ and in females at $\frac{100\text{–}212}{55\text{–}102}$.

OSSERVAZIONI CLINICHE SU UNA NUOVA SOSTANZA AD AZIONE ECCITANTE CENTRALE (CLINICAL OBSERVATIONS ON A NEW SUBSTANCE WITH CENTRAL NERVOUS SYSTEM STIMULATING ACTION).

Morpurgo, C. V. *Minerva anest.* (It.) **22:** No. 3, 1956; through Ciba Literature Review **2:** 90 (March) 1957.

More than half the emergencies connected with anesthesia occur in the awakening phase. In order to shorten this phase, Ritalin (methyl phenidyl acetate hydrochloride) is now employed as a routine measure for all ambulant patients who are given an anesthetic and for those bed patients who have to be brought back to full consciousness as soon as possible after prolonged anesthesia. Following a short-acting intravenous anesthetic, the intravenous injection of 20 to 30 mg. of Ritalin causes the patient to wake up quickly and yet feel so completely at ease that he can sit up after only a few minutes without suffering from giddiness. All 19 patients in this group were able to go home unaccompanied less than thirty minutes after the Ritalin injection. Following anesthesia brought about by the use of fairly large doses of barbiturates or by combining the latter with other anesthetics, the intravenous injection of Ritalin (up to 50 mg.) restored cerebrocortical activity far more quickly than would normally have been the case. In all 21 patients, signs of anesthesia disappeared considerably faster than expected. Amnesia and drowsiness seldom lasted longer than five to ten minutes, and nausea or vomiting hardly ever occurred. There was virtually no effect on blood pressure or heart rate.

CLASSIFICATION OF DISABILITY IN THE CHRONICALLY ILL AND AGING.

Moskowitz, E., and McCann, C. B. *J. Chron. Dis.* **5:** 342 (March) 1957.

Medical diagnoses do not accurately reflect the functional capacity of the chronically ill or aged person. A physical profile system adapted from that of the Canadian and United States Armies is proposed as a method of disability evaluation. The physical condition (including diseases of the viscera and cerebral disorders), upper extremities, lower extremities, sensory components relating to speech, vision and hearing, excretory function and mental and emotional status are rated numerically in accordance with the severity of abnormalities or deviations, or lack of control. This profile system was applied to 115 residents of a county home, most of whom were between the ages of 55 and 85 years. Diseases of the cerebral, cardiac, or peripheral vascular system were by far the most numerous. The profile categories revealed the degree of functional disability that was not apparent from the medical classifications. For example, the summary of the classifications showed a preponderance of functional disability in the legs as compared with the arms, a fact that could not be gleaned from the diagnoses. This profile will be of assistance in the rehabilitation of elderly persons and will relieve paramedical personnel of the task of trying to interpret medical data and to judge thereby a patient's physical capabilities.

ARLIDIN IN THE TREATMENT OF PERIPHERAL VASCULAR DISEASES.

Murphy, H. L., and Klasson, D. H. *New York J. Med.* **57:** 1908 (June 1) 1957.

Arlidin (phenyl secondary butyl norsuprifen; nylidrin hydrochloride) in a dosage of 18 mg. daily for three months was used to treat 79 patients with peripheral vascular disease. A dosage of 36 mg. proved no more effective. After three months' treatment, patients who

responded were given placebos. Those who responded to placebos were dropped from the study. Twenty-six of the 36 patients with arteriosclerosis obliterans improved. Walking distance increased and nocturnal leg cramps disappeared. Four patients with intermittent claudication and 6 with rest cramps failed to improve. Ulcerative lesions in 9 of 17 patients healed in two to six months. Diabetic patients were not adversely affected. Claudication improved in 4 patients and ulcers in 1 patient with thromboangiitis obliterans. Two patients were not benefited. In 2 of 3 patients with abdominal aortic occlusion of long standing, rest pain was reduced, walking distance increased, and the sense of heaviness in the thighs reduced. Low back pain remained unaltered. Twenty-three of 32 patients with chronic venous insufficiency improved. The drug reduced pedal edema and improved the granulation tissue in patients with ulceration of the ankle. Edema was reduced in 1 man with elephantiasis but ulcerated areas above the ankles in this patient and in 1 other remained unchanged. Arlidin proved to have its greatest effect upon the vasculature of skeletal muscle. It increased the blood flow to this tissue and this resulted in the improvement of rest pain and intermittent claudication. Little change occurred in skin temperature, oscillometric readings, or peripheral pulses. Patients could be managed by the use of Arlidin with ease. The drug is worthy of further evaluation in the treatment of peripheral vascular diseases, particularly those involving skeletal muscle.

RELATION OF OVARIAN STROMAL HYPERPLASIA TO ENDOMETRIAL CARCINOMA.

Roddick, J. W., Jr., and Greene, R. R. *Am. J. Obst. & Gynec.* **73:** 843 (Apr.) 1957.

A summary of the literature implicating an ovarian change called stromal hyperplasia in the evolution or etiology, or both, of endometrial carcinoma is presented. Proponents of this concept found what appears to be a significant increase in the occurrence of this change in patients with carcinoma of the endometrium as opposed to those without. Microscopic changes in ovarian histology which lead to this diagnosis include increased cellularity with increased cytoplasm in stromal cells accompanied by enlargement and blunting of nuclei—a feature unlike that seen in the usual spindle-shaped variety. These changes, when marked, are similar to or the same as thecosis, either diffuse or patchy. Other important findings are cortical granulomas and a relative or absolute decrease in the amount of collagen expected in atrophic ovaries with the reciprocal increase in reticulum. It has been stated that these changes are more evident and more common in the ovaries of persons with endometrial carcinoma than in those without endometrial cancer. That work was based on ovaries from patients with carcinoma obtained at operation and those of the controls at autopsy. The present study includes 42 control cases and 40 carcinoma cases. The preparations from both groups were from fresh surgical specimens. Results of this study failed to confirm the previously reported findings, in that there was no significant difference between the ovaries of those with and those without endometrial cancer. It appears from the findings in the reported small group that no specific changes have yet been observed in ovaries from women with endometrial carcinoma which cannot also be found in equal degree in those without endometrial carcinoma. (From authors' summary and conclusions.)

SUGESTIONES PARA EL TRATAMIENTO DEL ATAQUE CEREBRAL AGUDO O ENCEFALOPATÍA HIPERTENSIVA. ASPECTOS NO QUIRÚRGICOS DEL MISMO (SUGGESTIONS AS TO TREATMENT OF THE ACUTE CEREBRAL ATTACK OF HYPERTENSIVE ENCEPHALOPATHY).

Rolla, E. H. *Prensa méd. argent.* **43:** 1860, 1956; through Ciba Literature Review **2:** 82 (March) 1957.

The following treatment is recommended for acute cerebral symptoms of hypertension, whether or not they are accompanied by edema or convulsions: 2.5 mg. of Serpasil should be injected intramuscularly every eight hours, and 15 to 20 cc. of a 1 per cent solution of

procaine intravenously every six hours. In addition, a 50 per cent solution of glucose with caffeine should be given intravenously in certain cases. The combination of Serpasil and procaine makes it possible, on one hand, to interrupt undesirable reflexes of arterial hypertension at their central point, the hypothalamus, and on the other hand, to inhibit the sympathetic ganglia by medicinal means. Hypertonic glucose solution was found to have little therapeutic effect on cerebral edema. The treatment described proved effective in all cases in which it was carried out. The diastolic pressure dropped from 130 or 140 to 70 or 80 mm. Hg in five to six days. Clinical symptoms, including those of a psychic nature, decreased. An increase in arterial diameter was objectively demonstrated with the aid of arteriograms. Improvement in cerebral blood flow was apparent in the electroencephalogram.

THE CLINICAL PROBLEM OF ACUTE CIRCULATORY FAILURE.

Sharpe, G. P.; Whitaker, H. T., and Parsons, W. H. *Surg., Gynec. & Obst.* **104:** 535 (May) 1957.

Cardiac arrest, although rare, has increased in incidence during the last few years. The criteria chosen are those of Berne: cardiac arrest is a potentially avoidable, usually reversible ventricular asystole, with or without fibrillation, precipitated by the effect of anesthesia alone, surgery alone, or of these two in combination. The increased incidence cannot be attributed to the performance of more extensive and more radical operations. A preoperative dose of atropine does not prevent it. Neither is it a sudden, unforseeable episode. Eight cases of cardiac arrest are summarized. Two of the patients were children, 1 patient was 52 years of age, and the remainder were in their seventies. All had been properly prepared and were carefully observed. Beside the fact that each had received a variety of drugs, no common denominator could be found that might account for the cardiac arrest. Preanesthetic medication included morphine, codeine, or Demerol, Pantopon and atropine, all within reasonable dosage limits. Anesthesia was induced by various technics and with various agents such as small doses of thiopental sodium, nitrous oxide, cyclopropane ether, or procaine hydrochloride locally. Cardiac arrest occurred at various times during performance of the procedure, and once preoperatively five minutes before administration of the anesthetic was begun. In 1 patient, recognition of the cardiac arrest was delayed, and in another there was an unwarranted delay in instituting resuscitation. These patients died within thirty-six and forty-four hours, respectively. In 6 patients, thoracotomy was promptly performed and resuscitation attempted by the use of cardiac massage and artificial respiration with oxygen. In addition, all known useful drugs were used. These patients responded promptly. Four left the hospital and remained well. Two died a few days later following operative procedures. It is proposed that cardiac arrest is the result of hypoxia with myocardial starvation, or the administration of drugs or anesthetic agents that injure the heart, or a combination of these. Although avoidance of cardiac arrest is always the objective, the surgeon must be prepared to deal with this emergency. He needs to be proficient in the technic for cardiac massage. Careful manipulation can diminish myocardial damage that frequently occurs as a result of cardiac massage, particularly if it is prolonged.

ENDOCRINE CHANGES WITH PROSTATIC CARCINOMA.

Sommers, S. C. *Cancer* **10:** 345 (Mar.–Apr.) 1957.

Prostatic cancer patients and noncancerous control patients, 223 each, were studied pathologically for alterations in the endocrine glands, and target organs. Benign prostatic hypertrophy was found in 80 per cent of the cancer patients and 45 per cent of the controls. Pituitary cell counts and changes found in the testicular tubules favored uninhibited estrogen as the factor stimulating benign hypertrophy and sometimes sclerotic prostatic atrophy. The prostatic cancer patients formed a heterogeneous group. There were pituitary indications of active neoplastic growth in only 2 of the 6 cases of microscopic early adenocarcinoma studied. Among 16 completely analyzed cases of invasive or metastasizing prostatic cancer, 63 per cent had (inferred) pituitary-adrenocortical hyperfunction, 25 per

cent had evidence of increased pituitary growth hormone, and 12 per cent manifested pituitary FSH-estrogen hypersecretion. Changes in other endocrine glands indicated that pituitary and adrenocortical hormones and estrogen of undetermined origin were important factors in the development and further growth of prostatic carcinoma. (From author's summary.)

DAS VERHALTEN DER ELEKTROPHORETISCHEN PROTEINFRAKTIONEN IN SERUM VON FRAUEN NACH GABEN VON ANDROGENEN UND OESTROGENEN HORMONEN (THE SERUM CONTENT OF ELECTROPHORETIC PROTEIN FRACTIONS IN WOMEN AFTER DOSES OF ANDROGENS AND ESTROGENS).

Studnitz, W. v., and Berezin, D. *Klin. Wchnschr.* **34:** 1239, 1956; through Ciba Literature Review **2:** 72 (March) 1957.

It has long been known that androgens exert an anabolic effect on protein metabolism, but little attention has thus far been paid to their influence on plasma or serum proteins. The authors studied the effects of androgenic and estrogenic hormones on the various serum protein fractions in women of child-bearing age and in those at the menopause. Following administration of androgens (methylandrostenediol, methyltestosterone, testosterone propionate) the α_2-globulin fraction shows a clear-cut increase in 90 per cent of cases. A rise in β_1- and β_2-globulin levels is also frequently observed. The albumin level drops in roughly two-thirds of the cases. The α-lipoproteins, too, are often reduced. In response to estrogens (ethinyl estradiol, diethylstilbestrol) the α_1-globulin level rises in 86 per cent of cases. The α_2-globulin value also increase in two-thirds of the test subjects, whereas the γ-globulin value falls in roughly half the cases. The α-lipoprotein level tends to rise. Consideration of various factors indicates that the primary effect of administered sex hormones is to influence the levels of globulins and/or albumins which, in turn, exert a secondary effect upon the lipoprotein concentration.

EFFECT OF CHLORPROMAZINE ON THE FUNCTION OF THE ENDOCRINE ORGANS.

Suzuki, M.; Kamio, K.; Yasuda, M.; Akiyama, S.; Mitani, K.; Oyama, T.; Sato, K., and Yamashita, T. *Endocrinol. japon.* **3:** 67, 1956; through Ciba Literature Review **2:** 71 (March) 1957.

Women at various stages of normal pregnancy, patients with toxemia of late pregnancy and postclimacteric women were given a total of nine intramuscular injections of 25 mg. of chlorpromazine on five successive days. Following administration of chlorpromazine, the excretion not only of pituitary, but also of chorionic gonadotropin decreased. The excretion of estrone, estradiol, estriol, pregnanediol, and 17-hydroxycorticoids also was reduced, whereas that of 17-ketosteroids was little affected. The decrease was particularly marked in cases in which the initial levels had been high. Chlorpromazine lowered the action of ACTH in stimulating the adrenal cortex after the ACTH had been administered by intravenous drip infusion. Also of interest was the observation that Friedman's pregnancy test yielded negative results when the rabbits used for the injection of the gonadotropin were under the influence of chlorpromazine. It may thus be concluded that this drug not only inhibits endocrine activity of cerebral origin, but also reduces the hormonal secretion of the adrenals and the placenta.

LES OEDEMES. PROBLEMES BIOLOGIQUES ET THERAPEUTIQUES (EDEMA. BIOLOGIC AND THERAPEUTIC PROBLEMS).

Vesin, P., and Cattan, R. *Sem. hôp. Paris* **33:** 67, 1957; through Ciba Literature Review **2:** 80 (March) 1957.

Reduction in the amount of circulating fluid, as occurs in edema, results in increased concentration of aldosterone in the blood. This hormone provokes sodium retention and thus helps to maintain the edema. The letting of a fairly large quantity of blood stimulates

overproduction of aldosterone, in the same way as an ascites puncture is soon followed by a return of the dropsy. Among the drugs used to increase the secretion of urine and to combat edema, prednisone occupies a special position insofar as it attacks the cause of the disorder. It inhibits secretion of aldosterone by the adrenal cortex and thus makes it possible for a considerable quantity of sodium to be excreted, since the extent to which these ions are reabsorbed in the renal tubules as a result of the action of aldosterone is greatly diminished. Experience has shown that in edema due to various causes—cirrhosis of the liver, cardiac diseases, nephroses, hepatitis, or malnutrition—prednisone breaks the vicious circle causing the persistence of edema. When edema is accompanied by hyponatremia, the blood sodium level may even rise. It is likely that prednisone inhibits the overproduction of aldosterone indirectly. Osmotic factors, as well as the drug's effect on water and electrolyte metabolism, probably play a part in this process. It is still not clear why prednisone fails to act in certain cases of edema.

DYSFUNCTIONAL UTERINE BLEEDING IN THE PREMENOPAUSAL AND MENOPAUSAL YEARS.

Wall, J. A., and Jacobs, W. M. *Am. J. Obst. & Gynec.* **73:** 985 (May) 1957.

Two hundred and twenty-two women 40 to 56 years of age, excluding postmenopausal women, seen in a two-year period with a diagnosis of functional uterine bleeding of undetermined cause were studied. In each the results of pelvic examination on admission were essentially normal. The therapy administered consisted of curettage and cervical biopsies in 106 patients, curettage in 76, and hysterectomy with or without adnexectomy and with or without vaginal repair in the remainder. Microscopic examination showed the endometrium to be proliferative in one-third, secretory in one-fourth, and hyperplastic in one-fifth of the patients. This compares with an incidence of hyperplasia of 13.9 per cent in a younger group previously reported. Among the 50 cases of endometrial hyperplasia, 33 were cystic, and 17 atypical, with adenocarcinoma in 6 of the latter. Unopposed estrogen stimulation appeared to be of more consequence in the older group than in the younger. Among the patients with atypical endometrial hyperplasia, 6 were below age 47 and 11 were above this age, 7 of the latter being more than 50 years old. This condition appears to become more prevalent with a late menopause. Of the endometria, 25.8 per cent were progestational as compared with 21 per cent among younger women in an earlier report. The authors believe that atypical hyperplasia should be considered a premalignant lesion. Benign cystic hyperplasia should cause no alarm unless bleeding persists or recurs after curettage. An organic pathologic change was demonstrated as a possible cause of bleeding in 30.2 per cent of 222 women. Multiple uterine myomas were most frequently found (28 patients) and other conditions included adenomyosis, endometriosis, endometrial and endocervical polyps, atypical hyperplasia, adenoma of the endometrium, invasive squamous-cell carcinoma of the cervix, and carcinoma in situ of the cervix. The 9 cases of malignancy (4.5 per cent) were previously unsuspected. The thought is presented that perhaps some carcinogenic agent may precipitate abnormal bleeding. A patient with irregular premenopausal or menopausal uterine bleeding should be carefully screened by ruling out exogenous steroids and by careful pelvic examination. When indicated, the examination should include one or all of the following: cervical biopsy, Papanicolaou smears, or endometrial biopsy. If the results are negative, the patient should have a fractional diagnostic curettage with multiple biopsies of the cervix and careful examination under anesthesia. The discovery of organic pathologic changes as the cause of the bleeding calls for immediate appropriate treatment. If the results of all tests remain negative, the patient should continue under observation. If bleeding recurs, pelvic exploration with hysterectomy and adnexectomy should probably be performed. The authors believe that the term "functional uterine bleeding" is not applicable to patients in the premenopausal and menopausal years. In a large percentage of such patients an organic pathologic condition will be found. They point out that abnormal bleeding, even in the absence of organic pathology, may bear an ultimate

relationship to endometrial carcinoma. McKay observed that endometrial carcinoma bears a histochemical relationship to progestational endometrium. This, together with the finding that a high percentage of patients with a "bloody menopause" have a progestational endometrium, may indicate that this type of endometrium does not mean that ovulation has occurred. Rather, it may mean that a progesterone-like hormone is involved in the production of a "bloody menopause" and may eventually cause the development of endometrial carcinoma.

VAGINAL BLEEDING AFTER ARTIFICAL AMENORRHEA.

Woodruff, J. D., and Prystowsky, H. *Obst. & Gynec.* **9:** 444 (Apr.) 1957.

A study was conducted of 165 patients who had bleeding twelve months or more after amenorrhea induced by surgery or radiation for a benign pathologic process. Among them diagnostic study showed 43 malignant lesions (39 carcinomas of the cervix and 4 fundal cancers), and 122 benign conditions. The 25 per cent incidence of carcinoma was approximately 10 per cent higher than in a group of 574 cases of bleeding following the natural menopause that were previously investigated. The duration of amenorrhea, age at last menses, and the duration of bleeding were not related to the incidence of cancer. The duration, amount and intermittency of bleeding did not vary greatly between the two groups. In the benign group, the pathologic changes present in the numbers specified were: none, 103; endometrial hyperplasia, 4; myoma of the uterus, 4; cervical polyp, 3; urethral caruncle, 2; granuloma of the cervix, 2; pyometra, 2; and endometrial polyp, 2. The method of inducing amenorrhea and the rates of occurrence of subsequent malignancy were as follows: subtotal hysterectomy, 110 patients (32 per cent malignancy); bilateral adnexectomy, 13 patients (23 per cent malignancy); intrauterine radium, 18 patients (11 per cent malignancy); and roentgen-ray therapy, 24 patients (12.5 per cent malignancy). The cervical carcinomas were treated with radiation therapy except for 2 in Stage 0 in which cases the stumps were removed. Of the fundal carcinomas, 2 were treated by intrauterine radium and then total abdominal hysterectomy, and 1 with roentgen-ray therapy. The fourth was a hematometra secondary to almost complete cervical stenosis following roentgen-ray therapy for benign menopausal bleeding. The benign cases were treated by dilatation and curettage with biopsy of the cervix, hysterectomy in 6 instances, intrauterine radium therapy in 3 patients, and removal of the cervical stump originally in 1 patient and during the follow-up period in 3 others. The 32 per cent incidence of carcinoma among the patients with cervical stumps emphasized the advisability of performing total hysterectomy rather than the partial procedure. The study showed, through the finding of 3 carcinomas of the cervix among 13 patients so treated, that the removal of both tubes and ovaries without removal of the uterus is rarely, if ever, indicated. The 12.5 subsequent malignancy rate among the 42 patients in whom amenorrhea was induced by the use of roentgen-ray therapy strengthened the opinion that its use should probably be restricted to the poor-risk patient, and that hysterectomy is preferable in patients in good physical condition. The study indicated the value of preoperative biopsy of the cervix as a routine procedure.

NEWS AND NOTICES

USPHS BIBLIOGRAPHY ON AGING

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